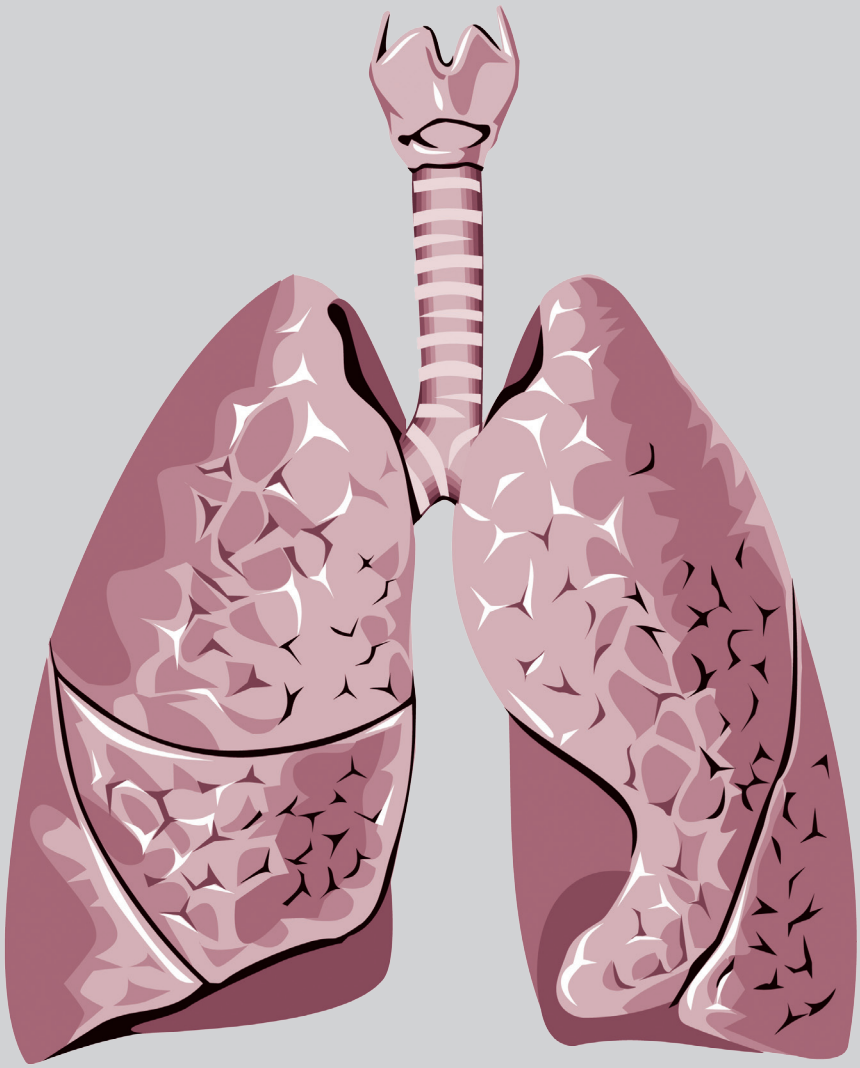
ISSN 1023-9855

Thoracic Medicine

Volume 35 • Number 2 • June 2020



The Official Journal of

Taiwan Society of Pulmonary and Critical Care Medicine

Taiwan Society of Sleep Medicine

Taiwan Society for Respiratory Therapy

Taiwan Society of Tuberculosis and Lung Diseases

Thoracic Medicine

The Official Journal of
Taiwan Society of Pulmonary and Critical Care Medicine
Taiwan Society for Respiratory Therapy
Taiwan Society of Sleep Medicine
Taiwan Society of Tuberculosis and Lung Diseases

Thoracic Medicine

The Official Journal of
Taiwan Society of Pulmonary and Critical Care Medicine
Taiwan Society for Respiratory Therapy
Taiwan Society of Sleep Medicine
Taiwan Society of Tuberculosis and Lung Diseases

Volume 35
Number 2
June 2020

CONTENTS

Progression-Free Survival of NSCLC Patients Receiving Low-Dose versus a Standard Dose of EGFR-TKI

Hsing-Chun Chen[1], Shu-Lan Hsu[1], I-Hung Chen[1], Yi-Chun Chu[1], Ke-Chin Fang[1], Kuo-Sheng Fan[1], Chun-Liang Lai[1,2]

Background: Patients with NSCLC sensitive to tyrosine kinase inhibitors (TKI) targeting epidermal growth factor receptor (EGFR) may use lower doses of TKI for various reasons. The treatment outcome in terms of progression-free survival (PFS) of patients receiving a dose reduction of first-generation EGFR-TKIs has not been reported in a real-world population. Here, we evaluate whether PFS was compromised due to dose titration in patients receiving gefitinib or erlotinib.

Methods: A retrospective cohort study was conducted and patients with advanced NSCLC sensitive to EGFR-TKI were recruited. Patients whose dose of TKI was titrated two-thirds or less were assigned to the low-dose (LD) group. The standard-dose (control) group included patients receiving 250 mg of gefitinib or 150 mg of erlotinib daily during the whole course of treatment, and they were matched by sex and age with the LD group. The primary outcome was PFS. The secondary outcome was overall survival (OS).

Results: The LD group included 20 patients and the control group had 80 patients. The median PFS was 15.4 months in the LD group and 9.3 months in the control group (HR: 0.45, 95% CI: 0.29-0.71; *p*=0.0018). The median OS was 31.5 months in the LD group and 31.4 months in the control group (HR: 0.99, 95% CI: 0.49-1.98; *p*=0.98). In the subgroup of gefitinib treatment, the median PFS was 15.4 months in the LD group and 8.1 months in the control group (HR: 0.35, 95% CI: 0.2-0.63; *p*=0.0029). Among patients receiving erlotinib, the median PFS was 14.3 months in the LD group and 12.1 months in the control group (HR: 0.67, 95% CI: 0.32-1.38; *p*=0.2747). Median OS was similar in the LD group and the control in both subgroups of gefitinib or erlotinib treatment.

Conclusion: This study found that a lower dose of first-generation EGFR-TKI is a non-inferior treatment strategy for NSCLC patients sensitive to EGFR-TKI. Larger-scale prospective studies would be needed to confirm this finding. ***(Thorac Med 2020; 35: 44-51)***

Key words: EGFR-TKI, gefitinib, erlotinib, low dose, optimum biologic dose

[1]Division of Pulmonology and Critical Care, Department of Internal Medicine, Buddhist Dalin Tzu Chi Hospital;
[2]School of Medicine, Tzu Chi University
Address reprint requests to: Dr. Chun-Liang Lai, Division of Pulmonology and Critical Care, Department of Internal Medicine, Buddhist Dalin Tzu Chi Hospital, No. 2, Min-Sheng Road. Dalin Town, Chiayi, Taiwan, R.O.C.

Introduction

Tyrosine kinase inhibitors (TKIs) of epidermal growth factor receptor (EGFR) are now the standard treatment for non-small-cell lung cancers (NSCLC) with sensitizing mutations [1]. However, the optimal dose of EGFR-TKI remains unsettled. There are different strategies for dose selection in the commercialization of TKIs. For example, 150 mg of erlotinib is at its maximal tolerated dose in a clinical trial [2], while 250 mg of gefitinib is set at the submaximum tolerated dose [3] or supposed optimum biological dose [4], which implies giving a higher dose fails to improve outcomes further [5]. In 2 phase I trials, gefitinib was administered once daily for 14 consecutive days every 28 days 6-7. A partial response was observed in 22% to 25% of patients and stable disease in 9% to 19% of patients. The response rates in such a protocol are roughly equal to the response rates in non-selective NSCLC patients in Western populations having daily EGFR-TKI [6-7]. Although daily regular dosing is recommended currently, some reports have shown that a lower dose, longer interval, or pulse therapy may also be effective under certain conditions, such as in patients with hepatotoxicity or leptomeningeal carcinomatosis [8-9]. Seki *et al*. reported a modified treatment schedule of gefitinib of 250 mg every 5 days for a patient with severe hepatotoxicity after daily administration [8]. The patient achieved nearly complete remission with this schedule. Based on pharmacokinetic studies of phase I trials for erlotinib [2] and gefitinib [4], 25 mg of erlotinib should have an expected mean trough steady state concentration similar to 250 mg of gefitinib. In a cell line study, Yeo *et al*. found that EGFR-mutated NSCLC cells were inhibited by similar concentrations of gefitinib and erlotinib in vitro 10. This result was supported by their clinical data, as the authors identified 7 patients who received 25 mg of erlotinib and reported that 5 of them (71.5%) had a partial response. The median progression-free survival (PFS) was 17 months. With a dose of 25 mg, erlotinib achieved a response rate and PFS similar to 250 mg of gefitinib or 150 mg of erlotinib. Benjamin *et al*. in a retrospective study, also reported sustained disease control in patients who received 50-75 mg of erlotinib [11].

Furthermore, whether some drug-drug interactions would influence treatment outcome remains a concern. For example, the US Food and Drug Administration has warned that gastric secretion inhibitors decreased the concentration-time curve and maximum plasma concentration of erlotinib and gefitinib in pharmacokinetic studies [12-13].

In clinical practice, some patients have received a lower dose of EGFR-TKI for various reasons, including adverse events or economic considerations. This was especially reported for afatinib, a second-generation EGFR-TKI that has irreversible binding and a higher percentage of dose reduction at the approved starting dose [14]. However, the treatment outcome of patients undergoing dose reduction with first-generation EGFR-TKIs has not been reported in a real-world population. Whether the PFS would be impaired due to dose adjustment, or unaffected or even better to support the above theory may need further clarification.

Methods

This retrospective cohort study was conducted in a regional teaching hospital. Medical records of patients with NSCLC from Janu-

ary 2009 to December 2015 were reviewed. The inclusion criteria were patients with stage IV adenocarcinoma whose tumors were either tested to have sensitizing mutations of EGFR using highly sensitive methods or clinically responsive to EGFR-TKI according to Jackman's criteria [15]. Patients who had recurrent NSCLC after a curative surgery were excluded. Patients enrolled were assigned to a low-dose (LD) group or a standard-dose (control) group. "Standard dose" is defined as receiving 250 mg of gefitinib or 150 mg of erlotinib daily during the whole treatment course. Patients with a TKI dose reduction to two-thirds or less were assigned to the LD group. Age and sex among patients in both groups were well matched. According to institutional guidelines, the patients underwent computed tomography and bone scans every 3 months for tumor evaluation, and magnetic resonance imaging of the brain to confirm any suspicious brain metastasis status or whether the patients were symptomatic. The response evaluation was based on RECIST criteria (version 1.1) [16]. Mismatch of the response evaluation by the clinician and radiologist would be discussed in a lung cancer multimodality conference at the institution to reach consensus. All images and clinical data were reviewed by the principal investigator and another senior pulmonologist.

The primary outcome was PFS, and the secondary outcome was overall survival (OS). This study was approved by the Institutional Review Board of Buddhist Dalin Tzu Chi Hospital.

Results

Enrollment and Patient Characteristics

The data of 100 patients that met the inclusion criteria were analyzed, including 20 patients with a titrated dose and 80 patients with a full dose of TKI treatment. In the LD group, the mean dose was 105 mg/day for erlotinib and 150 mg/day for gefitinib. Baseline demographic characteristics with regard to age and sex were balanced between the LD and control groups (Table 1). All patients in the LD group had more than 3 months of low-dose treatment and 70% (14 in 20) of the patients received low-dose TKI for more than half of the treatment period. There were more L858R mutations in the control group (45%) than in the LD group (20%). Most of the patients using LD treatment had experienced intolerable side effects with the standard dose (n=18, 90%). The most common side effect was skin eruptions or carbuncles (60%). Only 1 patient in the LD group had grade 3 hepatitis. No patients in the LD group resumed a standard dose of TKI when their disease progressed. In the control group, 46 out of 80 patients (57.5%) had side effects. Among these 46 patients, 28 (60%) had skin eruptions or carbuncles. One fourth (5/20) of the patients in the LD group and 26.3% (21/80) in the control group had a proton pump inhibitor (PPI) for clinical needs during their TKI treatment course.

Progression-Free Survival and Overall Survival

The median PFS was 15.4 months in the LD group and 9.3 months in the control group (hazard ratio (HR): 0.45, 95% confidence interval (CI): 0.29-0.71; p=0.018) (Figure 1). In patients with an EGFR exon 19 deletion or exon 21 L858R mutations, the median PFS was 16.1 months in the LD group and 8.9 months in the control group (HR: 0.36, 95% CI: 0.20-0.67; p=0.0074).

The median OS was 31.5 months in the LD

Table 1. Baseline Characteristics of the Patients

	Low dose (n=20)	Control (n=80)
Sex % (n)		
Male	50% (10)	50% (40)
Female	50% (10)	50% (40)
Age, years		
Mean (SD)	69.9 (11.8)	64.9 (11.2)
Cigarette smoking % (n)	25% (5)	38.8% (31)
WHO performance status % (n)		
0	5% (1)	16.2% (13)
1	55% (11)	53.7% (43)
2	20% (4)	25% (20)
3	20% (4)	3.7% (3)
4	0% (0)	1.2% (1)
Metastatic disease % (n)		
Brain	30% (6)	32.5% (26)
Liver	5% (1)	13.8% (11)
Bone	50% (10)	57.5% (46)
Lung	65% (13)	73.8% (59)
Adrenal gland	0% (0)	8.8% (7)
Other	5% (1)	12.5% (10)
EGFR TKI % (n)		
Erlotinib	55% (11)	40% (32)
Gefitinib	45% (9)	60% (48)
EGFR mutation % (n)		
Deletion of exon 19	25% (5)	26% (21*)
L858R mutation	20% (4)	45% (36*)
Other^{+}	0% (0)	2.5% (2)
Unknown	55% (11)	27.5% (22)

*One patient had both a deletion of exon 19 and L858R

$^{+}$G719x, and L861Q

group and 31.4 months in the control group (HR: 0.99, 95% CI: 0.49-1.98; p=0.98) (Figure 2). In the subgroup of gefitinib treatment, the median PFS was 15.4 months in the LD group and 8.1 months in the control group (HR: 0.35, 95% CI: 0.2-0.63; p=0.0029) (Figure 3). In patients receiving erlotinib, median PFS was 14.3 months in the LD group and 12.1 months in the control group (HR: 0.67, 95% CI: 0.32-1.38; p=0.2747) (Figure 4). Median OS in the LD and control groups was 31.5 and 31.4 months (HR: 1.13, 95% CI: 0.40-3.16; p=0.81), respectively, in the subgroup of erlotinib treatment, and 35 and 29 months (HR: 0.87, 95% CI: 0.33-2.25; p=0.78),

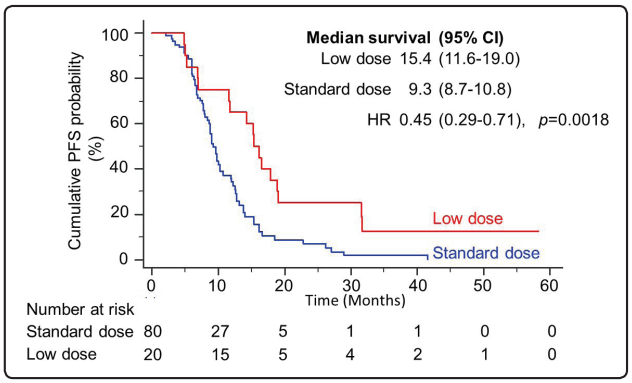


Fig. 1. Kaplan-Meier Plot of the Progression-Free Survival of Patients with a Low Dose and Those with a Standard Dose of EGFR-TKIs. Median PFS of the LD group: 15.4 months; the control group: 9.3 months (HR: 0.45, 95% CI: 0.29-0.71; p=0.0018).

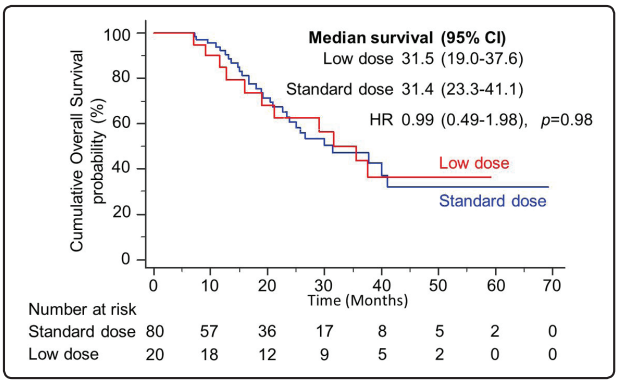


Fig. 2. Kaplan-Meier Plot of the Overall Survival of Patients with a Low Dose and Those with a Standard Dose of EGFR-TKIs. Median OS of the LD group: 31.5 months; the control group: 31.4 months (HR: 0.99, 95% CI: 0.49-1.98; p=0.98).

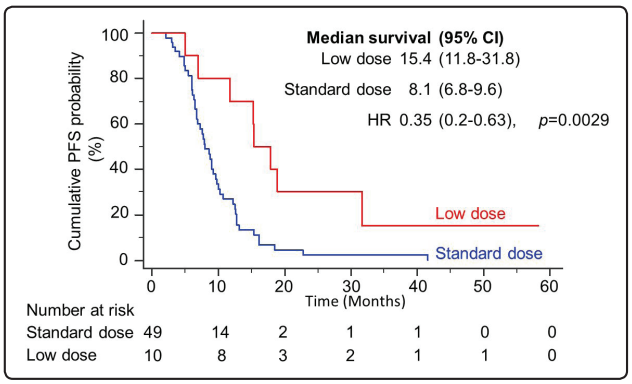


Fig. 3. Kaplan-Meier Plot of the Progression-Free Survival of Patients with a Low Dose and Those with a Standard Dose of Gefitinib. Median PFS of the LD group: 15.4 months; the control group: 8.1 months (HR: 0.35, 95% CI: 0.2-0.63; p=0.0029).

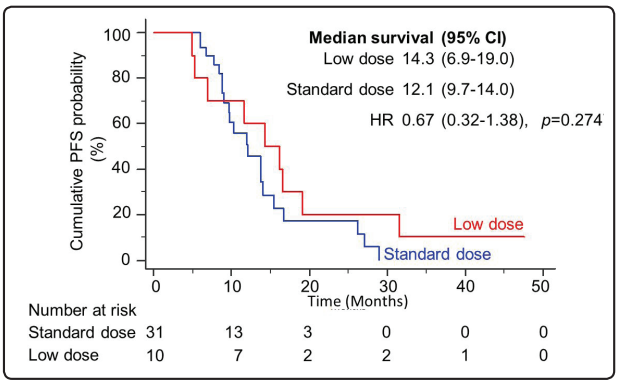


Fig. 4. Kaplan-Meier Plot of the Progression-Free Survival of Patients with a Low Dose and Those with a Standard Dose of Erlotinib. Median PFS of the LD group: 14.3 months; the control group: 12.1 months (HR: 0.67, 95% CI: 0.32-1.38; p=0.2747).

respectively, in the subgroup of gefitinib treatment. The median PFS in the LD group was 14.2 months for those who received erlotinib, and 15.3 months for those who received gefitinib (HR: 0.73, 95% CI: 0.28-1.90; p=0.5219). The median PFS in the control group was 12 months for those who received erlotinib and 8 months for those who received gefitinib (HR: 1.92, 95% CI: 1.18-3.10; p=0.01). The median OS in the low-dose group was 31.5 months for those who received erlotinib, and 35.5 months for those who received gefitinib (HR: 0.92, 95% CI: 0.28-3.03; p=0.9029). Patients in both groups who received a PPI and EGFR-TKIs concomitantly showed no difference in both PFS and OS.

Central Nervous System (CNS) and Non-CNS progression

Six out of 20 (30%) patients in the LD group and 26 out of 80 (32.5%) in the control group had CNS metastasis at the beginning of EGFR-TKI treatment. Of those patients with CNS metastasis, 2 (33.3%) in the LD group and

10 (38.5%) in the control group had CNS failure on disease progression. Of those who had no CNS metastasis before EGFT-TKI treatment, none in the LD group and 11 out of 54 (20.4%) in the control group were found to have CNS metastasis after TKI treatment.

Subsequent Therapies

In the LD group, 50% of patients received chemotherapy, 5% received another EGFR-TKI, and 30% received supportive care after disease progression. In the control group, 73% of patients received chemotherapy, 11% received another EGFR-TKI, and 16% received supportive care after disease progression. No patient in either group received a third-generation EGFR-TKI as subsequent salvage therapy.

Discussion

Our study found that a lower dose of first-generation EGFR-TKI treatment is a non-inferior strategy for patients who are sensitive to EGFR-TKI. There was no difference in OS between the LD and control groups. In the sub-group analysis, patients who received low-dose gefitinib had better PFS than those who received a standard dose. A trend toward better PFS using low-dose erlotinib was also observed, but this was non-significant statistically. There was no difference in OS between the low-dose and standard-dose group among patients that received erlotinib or gefitinib.

Since the approved dose of erlotinib and gefitinib is set at its maximal tolerated dose and sub-maximal tolerated dose, respectively, the optimum biological dose should be lower. Our results support an optimum biological dose of erlotinib and gefitinib below the standard dose, and the efficacy of both as such is non-inferior.

The better PFS of patients who received lower-dose gefitinib support the theory of the delayed emergence of resistant clones put forth by Chmielecki *et al.*, who used paired isogenic cell lines that were sensitive and resistant (T790M-containing) to afatinib and erlotinib to examine the behavior of NSCLC [17]. In their study, the drug-resistant cells grew more slowly than the sensitive cells (average~1.22 times). The authors then generated a mathematical prediction model and showed that a lower dose of EGFR-TKI combined with high-dose pulse therapy could delay the onset of T790M resistance in cell line settings. Our study used a retrospective cohort design and lacked a comprehensive resistance mechanism profile. Larger-scale prospective studies would be needed to confirm the findings.

Gastric secretion inhibitors have shown a drug-drug interaction with erlotinib and gefitinib by affecting gastric pH in pharmacokinetic studies [12-13]. However, 2 retrospective studies that analyzed patients given erlotinib or gefitinib with gastric secretion inhibitors showed no difference in PFS or OS [18-19]. Our patients had a relatively short course of PPI treatment compared with the duration of EGFR-TKI treatment. Only 5 patients in the LD group and 21 in the control group received PPI. Most patients received about 4 months of PPI use. Only 3 patients in the control group received 6 months of PPI treatment and 2 in the LD group received 9 months of PPI use. There was no difference in PFS and OS in both groups in our study.

In a previous study, 25 mg erlotinib yielded a response rate and PFS similar to 150 mg erlotinib. In our study, the LD group also showed a PFS and OS that was non-inferior to the standard-dose group. However, the PFS benefit of erlotinib in the LD group was not as evident

as that of gefitinib. One explanation might be the "lower dose" of erlotinib we used was still above its optimum biological dosage. Since 25 mg of erlotinib is equivalent to 250 mg of gefitinib [10], an even lower dose of erlotinib may be needed to delay the emergence of the resistant clone.

It is highly concerning that a lower-dose TKI might cause an insufficient CNS concentration and be prone to causing early CNS progression. In our study, the CNS progression rates in patients who had CNS metastases at the start of EGFR-TKI treatment were similar in both groups. We thought this may be due to a higher proportion of erlotinib use in the LD group (83% in the LD group versus 46% in the standard-dose group). Yoshida *et al*. reported that the incidence of CNS progression during erlotinib treatment was lower than that during gefitinib treatment [20]. The difference was attributed to the higher penetration rate of erlotinib across the blood brain barrier [21-23].

In our study, 2 of 6 patients who had CNS metastasis at the start of EGFR-TKI treatment developed CNS progression. These 2 patients received erlotinib. One patient underwent whole brain radiotherapy, but leptomeningeal metastasis occurred 19 months later. The other patient did not undergo brain radiotherapy, but the CNS metastasis had a partial response during the first 3 months when the patient received daily erlotinib. CNS progression occurred 16 months later. Two of the other 4 patients who did not develop CNS progression received brain radiotherapy with EGFR-TKI treatment. Brain radiotherapy may lower the incidence of CNS progression when using a lower-dose EGFR-TKI, but our cohort was not large enough to substantiate this.

This study has several limitations. In all, 55% of patients in the LD group and 27% in the standard-dose group had an unknown EGFR mutation status. Thus, we used Jackman criteria and imaging studies as surrogates for having an EGFR-TKI sensitive mutation. We did not have tissue proof of the emergence of T790m. Although 90% of the patients received a lower dose due to intolerable side effects, our study was unable to conclude whether having a "side effect" was a predictor for gaining an advantage from a lower-dose strategy.

Conclusion

This study showed that low-dose first-generation EGFR-TKI treatment is a non-inferior strategy for patients who are sensitive to EGFR-TKI. The better PFS in the LD group of gefitinib-treated patients supports the theory of a delayed emergence of a resistant clone. A trend toward a better PFS with the use of a lower dose of erlotinib was also observed. Larger-scale prospective studies would be needed to confirm this finding.

References

1. Network NCC. Non-Small Cell Lung Cancer (Version 4.2016). 2016.
2. Hidalgo M, Siu LL, Nemunaitis J, *et al*. Phase I and pharmacologic study of OSI-774, an epidermal growth factor receptor tyrosine kinase inhibitor, in patients with advanced solid malignancies. J Clin Oncol 2001; 19: 3267-79.
3. Sharma SV, Bell DW, Settleman J, *et al*. Epidermal growth factor receptor mutations in lung cancer. Nat Rev Cancer 2007; 7: 169-81.
4. Baselga J, Rischin D, Ranson M, *et al*. Phase I safety, pharmacokinetic, and pharmacodynamic trial of ZD1839, a selective oral epidermal growth factor receptor tyrosine kinase inhibitor, in patients with five selected solid tumor

types. J Clin Oncol 2002; 20: 4292-302.
5. Marshall JL. Maximum-tolerated dose, optimum biologic dose, or optimum clinical value: dosing determination of cancer therapies. J Clin Oncol 2012; 30: 2815-6.
6. Ranson M, Hammond LA, Ferry D, *et al*. ZD1839, a selective oral epidermal growth factor receptor-tyrosine kinase inhibitor, is well tolerated and active in patients with solid, malignant tumors: results of a phase I trial. J Clin Oncol 2002; 20: 2240-50.
7. Nakagawa K, Tamura T, Negoro S, *et al*. Phase I pharmacokinetic trial of the selective oral epidermal growth factor receptor tyrosine kinase inhibitor gefitinib ('Iressa', ZD1839) in Japanese patients with solid malignant tumors. Ann Oncol 2003; 14: 922-30.
8. Seki N, Uematsu K, Shibakuki R, *et al*. Promising new treatment schedule for gefitinib responders after severe hepatotoxicity with daily administration. J Clin Oncol 2006; 24: 3213-4; author reply 4-5.
9. Grommes C, Oxnard GR, Kris MG, *et al*. "Pulsatile" high-dose weekly erlotinib for CNS metastases from EGFR mutant non-small cell lung cancer. Neuro Oncol 2011; 13: 1364-9.
10. Yeo WL, Riely GJ, Yeap BY, *et al*. Erlotinib at a dose of 25 mg daily for non-small cell lung cancers with EGFR mutations. J Thorac Oncol 2010; 5: 1048-53.
11. Lampson BL, Janne PA, Oxnard GR, *et al*. Reduced-dose versus full-dose erlotinib for advanced EGFR-mutant non-small cell lung carcinoma (NSCLC): A retrospective analysis. J Clin Oncol 2015; 33: suppl; abstr 8074.
12. The US Food Drug Administration. TARCEVA (Erlotinib) PRESCRIBING INFORMATION. 2015. Nov 29.
13. The US Food Drug Administration. IRESSA (Gefitinib) PRESCRIBING INFORMATION 2015.
14. Yang JC, Sequist LV, Zhou C, *et al*. Effect of dose adjustment on the safety and efficacy of afatinib for EGFR mutation-positive lung adenocarcinoma: post hoc analyses of the randomized LUX-Lung 3 and 6 trials. Ann Oncol 2016; 27: 2103-10.
15. Jackman D, Pao W, Riely GJ, *et al*. Clinical definition of acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors in non-small-cell lung cancer. J Clin Oncol 2010; 28: 357-60.
16. Eisenhauer EA, Therasse P, Bogaerts J, *et al*. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45: 228-47.
17. Chmielecki J, Foo J, Oxnard GR, *et al*. Optimization of dosing for EGFR-mutant non-small cell lung cancer with evolutionary cancer modeling. Sci Transl Med 2011; 3: 90ra59.
18. Saeki S, Sakaki J, Morioka J, *et al*. The influence of gastric secretion inhibitors on gefitinib therapy in patients with non-small cell lung cancer harboring epidermal growth factor receptor activating mutations. J Clin Oncol 2012; 30: suppl; abstr e18059.
19. Kumarakulasinghe NB, Syn N, Soon YY, *et al*. EGFR kinase inhibitors and gastric acid suppressants in EGFR-mutant NSCLC: a retrospective database analysis of potential drug interaction. Oncotarget 2016; 7: 85542-50.
20. Yoshida K, Kanda S, Shiraishi H, *et al*. Difference in central nerve system metastasis during gefitinib or erlotinib therapy in patients with EGFR-mutated non-small cell lung cancer: a retrospective study. J Thorac Dis 2019; 11: 1347-54.
21. Masuda T, Hattori N, Hamada A, *et al*. Erlotinib efficacy and cerebrospinal fluid concentration in patients with lung adenocarcinoma developing leptomeningeal metastases during gefitinib therapy. Cancer Chemother Pharmacol 2011; 67: 1465-9.
22. Togashi Y, Masago K, Masuda S, *et al*. Cerebrospinal fluid concentration of gefitinib and erlotinib in patients with non-small cell lung cancer. Cancer Chemother Pharmacol 2012; 70: 399-405.
23. Zhao J, Chen M, Zhong W, *et al*. Cerebrospinal fluid concentrations of gefitinib in patients with lung adenocarcinoma. Clin Lung Cancer. 2013; 14: 188-93.

Early Detection of Chronic Obstructive Pulmonary Disease in Patients with Coronary Artery Disease

Wei-Chun Huang[1], Chia-Hung Chen[1,4,5,8], Biing-Ru Wu[1], Lien-Cheng Hsiao[7], Hung-Jen Chen[1,4], Chih-Yu Chen[1], Wei-Chih Liao[1,5,6], Ping-Han Lo[1,7], Wen-Chien Cheng[1,2,6], Chih -Yen Tu[1,2,3], Wu-Huei Hsu[1,2,8]

Objectives: Chronic obstructive pulmonary disease (COPD) and coronary artery disease (CAD) usually coexist and share the same risk factors. Early diagnosis of COPD in patients with CAD allows for early intervention, which improves the prognosis. The purpose of this study was to determine a method for early detection of COPD in this target population.

Methods: In this single-center, observational, prospective study, outpatients with CAD (aged >40 years with a history of smoking) were evaluated. Each patient underwent a COPD assessment after coronary angiography. Data on age, smoking status, pack-year history of smoking, body mass index (BMI), and dyspnea score (Medical Research Council), and the results of a COPD assessment test (CAT) and pre- and post-bronchodilator spirometry were obtained.

Results: A total of 166 patients were included in the study, most of whom were men (92.7%). A definitive diagnosis of COPD was made by spirometry in 32 patients (19.3%). Sixteen (50%) and 16 (50%) patients were assigned to group A and B respectively. Statistically significant differences in age, pack-year history of smoking, body weight, BMI, C-reactive protein (CRP) levels, serum sodium levels, and symptoms such as cough and sputum (CAT scores) were observed between CAD patients with COPD and those without COPD. Multivariate analysis revealed that aged >60 years (P<0.001), a smoking history >30 pack-year (P=0.006), body weight <60 kg (P=0.04), sputum production (CAT score, Sputum ≧1) (P=0.01) and a lower serum sodium level (Na <135 mg/dl) (P=0.028) were independent clinical characteristics of COPD development in CAD patients.

Conclusion: Approximately 19.3% of our outpatients with CAD had COPD. It is important to evaluate for COPD in CAD patients with aged >60 years, a history of smoking >30 pack-years, body weight <60 kg, more sputum production, and a low serum sodium level. ***(Thorac Med 2020; 35: 52-63)***

Key words: chronic obstructive pulmonary disease, cardiovascular disease, COPD assessment test

[1]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, China Medical University Hospital, [2]School of Medicine, China Medical University, [3]Department of Life Science, National Chung Hsing University, [4]Department of Respiratory Therapy, China Medical University, [5]Graduate Institute of Clinical Medical Science, China Medical University, [6]Department of Internal Medicine, Hyperbaric Oxygen Therapy Center, China Medical University, [7]Division of Cardiology, Department of Internal Medicine, China Medical University Hospital, [8]Taiwan Clinical Trial Consortium for Lung Diseases (TCoC)

Address reprint requests to: Dr. Wen-Chien Cheng, Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, China Medical University Hospital, No 2, Yude Road, Taichung, Taiwan

Introduction

Chronic obstructive pulmonary disease (COPD) is an inflammatory disease of the lungs associated with progressive airflow limitation (AL) and punctuated by episodes of acute exacerbation. The inflammatory state associated with COPD is not restricted to the lungs, but also involves systemic circulation and can affect other organs. An increasing number of studies indicate that COPD is associated at a high frequency with coronary artery disease (CAD), congestive heart failure, and cardiac arrhythmias, independent of shared risk factors. Possible pathways include complex interrelationships between oxidative stress and chronic low-grade systemic inflammation, as well as shared risk factors such as age, cigarette smoking, and exposure to environmental pollutants [1-3].

Patients with COPD have subclinical left ventricular dysfunction related to arterial stiffness, and right ventricular dysfunction related to airway obstruction. Both right and left ventricular dysfunction are present in patients with mild obstruction of the airways, suggesting that cardiac comorbidities commence early in the development of COPD [4]. COPD is associated with a 2- to 3-fold increase in the risk of ischemic heart disease, stroke, and sudden death [3]. Patients with COPD have a greater mortality rate, a higher rate of rehospitalization, and poorer health status 1 year after a myocardial infarction [6]. Observational data suggest that slowing COPD progression may help in reducing cardiovascular morbidity and mortality, which are associated with more severe pulmonary symptoms [7]. Therefore, early detection of these 2 diseases and early treatment in pulmonary or cardiovascular clinics is very important.

The prevalence of AL in Japan, as observed in a Japanese study, indicates that 25% of outpatients with CAD have COPD, and it remains undiagnosed in almost all the cases [8]. In a Spanish study, AL was detected in 19% of patients with CAD [9]. These findings suggest that it is important to evaluate routinely for COPD in patients with CAD.

However, little is known about the prevalence of COPD in CAD outpatients with a history of smoking in Taiwan, and there are very limited data on the clinical characteristics of undiagnosed COPD in patients with CAD. The aims of our study were to 1) determine the prevalence of COPD in patients with CAD who need cardiac catheterization, and 2) point out some clinical clues that may be helpful in the early detection of COPD in patients with CAD in outpatient clinics.

Patients and Methods

Enrolled patients

This study was conducted at the outpatient department of the Division of Cardiology Medicine, China Medical University Hospital, which is a 2,146-bed community-based university hospital in Taichung, Taiwan. The study was approved by the China Medical University Hospital Internal Review Board (DMR102-REC1-066). Patients aged >40 years with a smoking history of ≥10 pack-years and a diagnosis of CAD (by coronary angiography [CAG]) were enrolled in the study. Any patient who had difficulty performing spirometry on the day of the study visit due to a respiratory infection with acute exacerbation was required to return when the exacerbation had resolved. Patients with a diagnosis of asthma, acute pulmonary

tuberculosis, interstitial lung disease, or bronchiectasis were excluded.

Study design

The study involved a prospective investigation of patients visiting the cardiac clinic of China Medical University Hospital from December 2013 to June 2014. Assessments were made during a single visit. Only those patients who had the ability to undergo spirometry and to complete the COPD assessment test (CAT) [10] questionnaire were selected to participate in the study; the Modified Medical Research Council (mMRC) Dyspnea Scale [11] score was determined during the visit. Predicted FEV_1 was calculated according to the formula used by the Lung Physiology Committee of the Taiwan Respiratory Society. AL was defined as a post-bronchodilator FEV_1/FVC ratio <0.70 [12]. All the blood tests were done before CAG. Demographic characteristics, details of concurrent diseases and medications used, mMRC dyspnea scores, and results of blood tests, CAG, CAT, and pre- and post-bronchodilator spirometry (FEV_1, FEV% predicted, FEV/FVC) were obtained.

Symptoms were quantified with both the CAT [10] (http://www.catestonline.org) and the mMRC Dyspnea Scale [11]. The CAT consists of 8 items, each of which is scored from 0 to 5. An overall score is calculated by adding the score from each item; the total score can range from 0 to 40. The mMRC Dyspnea Scale (score of 0 to 4) was developed by the American Thoracic Society as a modification of the originally proposed British Medical Research Council dyspnea index (scale of 1 to 5) [13]. We determined the distribution of COPD patients using the mMRC Dyspnea Scale and the CAT. According to the Global Initiative for Obstructive Lung Disease (GOLD) 2017 classification [14], patients were stratified by either the mMRC Dyspnea Score (0–1 vs ≥2) or the CAT score (<10 or ≥10), which resulted in 2 low-symptom categories (A and C) and 2 high-symptom categories (B and D). Exacerbation risk was assessed based on the patient's COPD exacerbation history (0–1 vs ≥2) in the previous year; patients were stratified into low-risk groups (A and B) or high-risk groups (C and D). An exacerbation was defined as an acute event characterized by a worsening of the patient's respiratory symptoms that exceeded normal day-to-day variations and led to a change in medication [14]. The number of exacerbations in the previous year was obtained from the patients' histories at the same time the mMRC and CAT scores were determined [15]. Finally, the patients with COPD were categorized into group A, B, C, or D on the basis of a combined symptom assessment: CAT or mMRC dyspnea scores and exacerbation risk according to the 2017 GOLD guidelines. Body mass index (BMI) was calculated by dividing weight in kilograms by the square of height in meters. Spirometry was conducted according to current international guidelines [16] by means of portable spirometers (Easy One NDD; Medical Technologies; Zurich, Switzerland). Reported values corresponded to those determined after the patients inhaled 200 mg of salbutamol. AL compatible with COPD was defined according to the GOLD guidelines as a post-bronchodilator $FEV_1/FVC < 0.7$ [17].

Statistical analysis

The data were analyzed using SPSS for Windows, version 17.0 (Chicago, IL, USA).

Continuous variables were reported as means ±SDs and were compared using 2-tailed Student's t tests. Categorical variables were reported as the numbers of patients and percentages. Differences between categorical variables were evaluated using Fisher's exact test. Multivariate analyses were performed to determine factors that were independently associated with CAD patients with COPD. Variables were entered into a final model using a stepwise multiple logistic regression analysis. All statistical tests were 2-sided; a P value ≤0.05 was considered significant. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated.

Results

Patient characteristics

The study population consisted of 166 subjects for whom spirometry data, CAT assessment results, mMRC Dyspnea Scale scores, and other clinical data were available. Most patients were men (n=154, 92.7%). COPD was diagnosed in a total of 32 patients (19.3%) on the basis of symptoms and spirometry results (GOLD guidelines). Patients with COPD were older than those without COPD (67.2±7.4 vs. 57.4±9.2 years; $p<0.001$). Compared to patients without COPD, patients with COPD weighed less (65.1±12.4 vs. 74.7±13.9 kg; $p=0.013$), had a lower BMI (24.3±3.8 vs. 27.3±3.7 kg/m^2; $p=0.013$), and had a longer smoking history (51.9 ±48.1 vs. 22.6±25.8 pack-years; $p=0.001$). The most commonly reported respiratory symptoms (e.g., chest tightness, chest pain, shortness of breath) were similar, and no significant differences in the incidence of other medical diseases were found between the 2 groups (Table 1).

Results of the pulmonary function test and symptoms questionnaire (CAT and mMRC Dyspnea Scale) for the CAD patients with or without COPD are shown in Table 2. Compared to the CAD patients without COPD, those with COPD had significantly poorer pulmonary function: FEV_1 (1.81±0.54 L), FVC (2.61±0.70 L), MMEF (1.11±0.49 L), and FEV_1/FVC (68.0% ±2.9%). Symptoms evaluated by questionnaire (CAT and mMRC Dyspnea Scale) were not significantly different between patients with and without COPD. However, the CAT score in CAD patients with COPD was slightly higher (9.13±5.49) than that in CAD patients without COPD (7.57±3.83) ($p=0.061$). The subgroup analysis of CAT scores showed that symptoms such as cough (1.19±1.03; $p=0.026$) and sputum (1.25±0.84; $p<0.001$) were significantly more frequent in the patients with COPD.

The group without COPD had higher B-type natriuretic peptide levels (1236.44±4432.44 pg/ml) than the group with COPD (752.60± 1286.35 pg/ml), although not significantly so ($p=0.556$). The C-reactive protein (CRP) level in CAD patients with COPD was higher (1.58 ±3.89 mg/dl) than that in those without COPD (0.62±1.23 mg/dl) ($p=0.017$). The serum sodium level was lower in the patients with COPD than in those without COPD (133.50±2.89 vs 138.04±2.60 mg/dl; $p=0.002$). No significant differences in other laboratory data were found between the 2 groups. All enrolled patients underwent CAG to determine CAD severity and the need for percutaneous coronary intervention. There was no obvious difference in CAD severity between the 2 groups (Tables 3 and 4).

The 32 patients (19.3%) with COPD were categorized into group A, B, C, or D according to 2017 GOLD guidelines. Sixteen patients (50%) were categorized into group A and 16 (50%) into group B; no patients were categorized into group C or D. We classified patients

Table 1. Characteristics of CAD Patients with or without COPD

	With COPD, n=32	Without COPD, n=134	*p-value*
Age (year)	67.2 ± 7.4	57.4 ± 9.2	<0.001
Height (cm)	163.0 ± 5.4	164.6 ± 7.0	0.394
Weight (kg)	65.1 ± 12.4	74.7 ± 13.9	0.013
BMI, kg/m ^{2}, mean ± SD	24.3 ± 3.8	27.3 ± 3.7	<0.001
Underlying disease (%)			
Osteoporosis	0 (0)	6 (4.5)	0.389
HTN	24 (75)	94 (70.1)	0.701
DM	18 (56.3)	50 (37.3)	0.16
Hyperlipidemia	24 (75)	88 (65.7)	0.474
Liver disease	4 (12.5)	8 (6.0)	0.365
GI disease	4 (12.5)	6 (4.5)	0.226
Renal disease	4 (12.5)	10 (7.5)	0.515
ESRD	2 (6.3)	6 (4.5)	0.766
Cancer	2 (6.3)	8 (6.0)	0.966
Psychiatric disease	6 (18.8)	12 (9.0)	0.258
Old CVA	0 (0)	8 (6.0)	0.316
Smoker (%)			
Ex	6 (18.8)	42 (31.3)	0.916
Current	26 (81.2)	92 (68.7)	
Smoking history, pack-years	51.9 ± 48.1	22.6 ± 25.8	0.001
Initial symptom (%)			
Chest tightness	18 (56.3)	58 (43.3)	0.236
Chest pain	6 (18.8)	22 (16.4)	0.800
SOB	2 (6.3)	2 (1.5)	0.168
Chest tightness + pain	6 (18.8)	32 (23.9)	0.859
Chest tightness + SOB	0 (0)	14 (10.4)	0.074
All	0 (0)	6 (4.5)	0.597

Data are shown as mean ± SD or number (%)

Acronyms:

BMI: body mass index, HTN: hypertension,

DM: diabetes, GI: gastrointestinal, ESRD: end stage renal disease,

CVA: cerebral vascular accident, SOB: shortness of breath

into 4 groups FEV_1 level, as determined by the spirometry test (GOLD 1: FEV_1 ≥80%, GOLD 2: 50% ≤FEV_1 <80%, GOLD 3: 30% ≤FEV_1 <50%, GOLD 4 FEV_1 <30%). Our patients were divided as follows: GOLD 1: n=8, 25%, GOLD 2: n=22, 68.8%, and GOLD 3: n=2, 6.2% (Table 5). Most of our CAD patients with COPD were in the early stages.

Clinical characteristics of undiagnosed COPD in CAD subjects

Using univariate analysis, the correlations

Table 2. Pulmonary Function Test and Questionnaire Results of CAD Patients with or without COPD

	With COPD, n=32	Without COPD, n=134	*p-value*
FEV_1(L)	1.81 ±0.54	2.55 ±0.66	<0.001
FVC(L)	2.61 ±0.70	3.06 ± 0.75	0.031
MMEF	1.11 ±0.49	2.86 ±1.02	<0.001
FEV_1/FVC (%)	68.0 ± 2.9	84.04 ± 5.30	<0.001
mMRC (%)	1.44 ± 0.81	1.36 ± 0.81	0.726
grade 0	4 (12.5)	18 (13.4)	0.577
grade 1	12 (37.5)	60 (44.8)	0.294
grade 2	14 (43.8)	46 (34.3)	0.213
grade 3	2 (6.3)	10 (7.5)	0.583
grade 4	0 (0)	0 (0)	
CAT	9.13 ± 5.49	7.57 ± 3.83	0.061
Cough	1.19 ± 1.03	0.79 ± 0.86	0.026
Sputum	1.25 ± 0.84	0.64 ± 0.73	<0.001
Chest tightness	2.06 ± 1.16	2.06 ± 1.10	0.990
Breathlessness	1.88 ± 1.43	1.82 ± 1.27	0.833
Limited activity	0.25 ± 0.76	0.22 ± 0.60	0.883
Confident leaving home	0.50 ± 1.24	0.55 ± 0.99	0.834
Sleep	1.06 ± 1.05	0.82 ± 0.79	0.227
Energy	0.88 ± 0.71	0.66 ± 0.64	0.091

Data are shown as mean ± SD or number (%)

Acronyms:

mMRC: Modified Medical Research Council Dyspnea Scale

CAT: COPD assessment test

Table 3. Coronary Angiography Results of CAD Patients with and without COPD

	With COPD, n=32	Without COPD, n=134	*p-value*
PCI (%)	30 (93.8)	110 (82.1)	0.249
Stent (%)	26 (81.3)	94 (70.1)	0.373
CAD (%)			
LM	0 (0)	6 (4.5)	0.597
LAD	14 (43.8)	58 (43.3)	0.962
LCX	6 (18.8)	30 (22.4)	0.813
RCA	8 (25.0)	34 (25.4)	0.965
Ramus	4 (12.4)	4 (4.4)	0.102

Data are shown as number (%)

Acronyms:

PCI: percutaneous coronary intervention, CAD: coronary artery disease

LM: left main artery, LAD: left anterior descending artery, LCX: left circumflex artery, RCA: right coronary artery, Ramus: ramus intermedius artery

Table 4. Clinical Laboratory Data of CAD Patients with and without COPD

	With COPD, n=32	Without COPD, n=134	*p-value*
WBC (x10^3/ul)	7.48 ± 2.38	7.85 ± 2.13	0.753
Neutrophil (%)	63.87 ± 1.93	61.16 ± 10.96	0.674
Hb (g/dL)	13.48 ± 1.99	14.19 ± 2.04	0.503
PLT (x10^3/ul)	248.25 ± 50.28	219.15 ± 48.85	0.256
BUN (mg/dL)	22.00 ± 12.00	21.06 ± 21.75	0.942
Cr (mg/dL)	1.66 ± 0.55	1.43 ± 2.17	0.838
Na (mmol/L)	133.50 ± 2.89	138.04 ± 2.60	0.002
K (mmol/L)	4.03 ± 0.32	3.85 ± 0.46	0.472
CPK (IU/L)	451.0 ± 540.87	237.60 ± 381.50	0.378
CKMB (ng/mL)	27.37 ± 36.21	10.98 ± 23.24	0.274
CHOL (mg/dL)	189.00 ± 31.58	177.50 ± 50.52	0.704
HDL (mg/dL)	56.90 ± 14.43	41.39 ± 11.35	0.086
BNP (pg/mL)	752.60 ± 1286.35	1236.44 ±4432.44	0.556
CRP (mg/dL)	1.58 ± 3.89	0.62 ± 1.23	0.017

Data are shown as mean ± SD

Acronyms:

HB: hemoglobin, PLT: platelet, BUN: blood urea nitrogen, Cr: creatinine, Na: sodium, K: potassium, CPK: creatine kinase, CKMB: creatine kinase-MB, CHOL: cholesterol, HDL: high-density lipoprotein, BNP: B-type natriuretic peptide, CRP: C-reactive protein

Table 5. CAD Patients with COPD Categorized into Groups A, B, C, or D Based on 2017 GOLD Guidelines

With COPD	n=32
Group	
Group A	16 (50%)
Group B	16 (50%)
Group C	0 (0%)
Group D	0 (0%)
GOLD	
GOLD I	8 (25%)
GOLD II	22 (68.8%)
GOLD III	2 (6.2%)
GOLD IV	0 (0%)

Data are shown as number (%)

Acronym:

GOLD: The Global Initiative for Chronic Obstructive Lung Disease

between the clinical characteristics of the CAD patients and COPD were evaluated in order to determine which variables played a significant role in early diagnosis of COPD, using univariate analysis (Table 6). A positive correlation was observed between COPD and advanced age (>60 years old) (OR: 7.28), higher serum CRP (>1.0 mg/dl) (OR: 2.886), lower serum sodium level (<135 mg/dl) (OR: 5.954), less body weight (<60 kg) (OR: 2.857), longer smoking history (>30 pack-years) (OR: 2.742), more cough symptoms (CAT score, cough ≥1) (OR: 3.514), and sputum symptoms (CAT score, sputum ≥1) (OR: 4.206). In multivariate analysis , age >60 years (OR: 10.876, 95% CI: 3.332 to 35.503, $p<0.001$), serum sodium <135 mg/dl (OR: 7.321, 95% CI: 1.246 to 43.036, $p=0.028$), body weight <60 kg (OR: 3.884, 95% CI: 1.066

Table 6. Univariate and Multivariate Analysis of Factors Associated with COPD in CAD Patients

Variables	Univariate analysis			Multivariate analysis		
	Odds Ratio for COPD	95% Confidence Interval	*p* Value	Odds Ratio for COPD	95% Confidence Interval	*p* Value
BW <60 kg	2.857	1.080-7.559	0.035	3.884	1.066-14.157	0.040
CAT score, cough ≧1	3.514	1.358-9.092	0.005	0.288	0.067-1.245	0.096
CAT score, sputum ≧1	4.206	1.626-10.876	0.001	4.718	1.449-15.360	0.010
Age >60 years old	7.280	2.804-18.904	<0.001	10.876	3.332-35.503	<0.001
CPR >1.0 mg/dl	2.886	1.138-7.321	0.026	2.771	0.803-9.554	0.107
Smoking >30 pack-year	2.742	1.224-6.143	0.01	4.824	1.563-14.895	0.006
Sodium <135 mg/dl	5.954	1.690-20.977	0.007	7.321	1.246-43.036	0.028

Acronyms:
BW: body weight, CAT: COPD assessment test, CRP: C-reactive protein

to 14.157, $p<0.040$), smoking history >30 pack-years (OR: 4.824, 95% CI: 1.563 to 14.895, $p<0.006$), and sputum ≥1 from the CAT score (OR: 4.718, 95% CI: 1.449 to 15.360, $p=0.01$) remained as independent predictive factors of COPD.

Discussion

COPD was present in 19.3% of the outpatients with CAD and a history of smoking; in most cases, COPD had not been diagnosed previously. The prevalence of COPD observed in our study is in agreement with that found in previous studies, which ranged from 19% to 25% in patients with CAD [8-9]. In most of our CAD patients with COPD, COPD was in the early stages. Significant differences in age, pack-year history of smoking, body weight, BMI, CRP levels, serum sodium levels, and symptoms such as cough and sputum production (data was collected through CAT) were observed between the CAD patients with COPD and those without COPD. Furthermore, being elderly (aged >60 years old), having a history of smoking (>30 pack-years), lower body weight (BW <60 kg), sputum production (CAT score, sputum ≥1) and a low serum sodium level (Na <135 mg/dl) were independent clinical characteristics of COPD in CAD patients.

Cardiovascular disease (CVD), especially CAD, is the leading cause of death in patients with COPD. CAD patients with COPD show a high prevalence of common risk factors for CVD, including smoking, a sedentary lifestyle, and a low socioeconomic status [18]. Several previous studies have reported that the burden of CVD is greater in patients with COPD. A large (n=11,493) retrospective study of the healthcare databases in Saskatchewan, Canada, reported an increased risk of arrhythmia, angina, acute myocardial infarction, congestive heart failure, and stroke in patients with COPD [7]. Smokers with AL have been shown to have

exaggerated subclinical atherosclerosis; therefore, middle-aged men who are susceptible to COPD may also be susceptible to vascular atherosclerosis from smoking, and atherosclerotic changes start early in the progression of COPD [19]. Patients with COPD were likely to be hospitalized with CVD and die over an average follow-up time of nearly 3 years. The relationship between COPD and CVD outcomes was stronger in adults <65 years of age. These data suggest that CVD risk should be monitored and treated with particular care in younger adults with COPD [20]. Patients with acute myocardial infarction and COPD have a substantially worse prognosis (in terms of mortality and health status) and require careful attention at the time of discharge from hospital and during follow-up [6]. Therefore, early detection of COPD in patients with CAD is very important. Based on our study results, some clinical clues may be useful in the early detection of COPD in patients with CAD.

Our results showed that CAD patients with COPD were older and had a longer smoking history. A study implied that in a geriatric population, older age and active smoking habits are independent risk factors for developing COPD. The incidence rate of AL was significantly higher for the 70–79- and 80–89-year-old cohorts than for the youngest age group [21]. Kojima S *et al* and Johannessen A *et al* found that COPD risk gradually increased with aging, and that there was a dose-response relationship between smoking and COPD risk [22-23]. A low BMI (<20) was found in 20% to 30% of patients with advanced COPD, and nutritional deficiency was an independent risk factor for mortality and hospitalization in patients with COPD receiving long-term oxygen therapy. The best prognosis was observed among overweight and obese patients with COPD [24]. Among our patients with CAD, body weight and BMI were lower in those with COPD than in those without. BMI <25 and comorbidity were predictors of all-cause and respiratory mortality in a cohort of COPD patients treated with long-term oxygen therapy [25].

COPD is a systemic inflammatory disease, and can adversely affect the arterial district. Patients with COPD tend to be at greater risk of atherosclerotic plaque formation and rupture. Platelet activation, coagulation, and oxidative stress are also possible mechanisms for the development of atherosclerosis in COPD patients [26].

An elevated CRP level has been shown to increase the risk of COPD almost 2-fold. This suggests an important interplay between systemic inflammation and airflow obstruction in the development of ischemic heart disease [27]. Our observation was similar to this finding, in that CVD patients with COPD had a higher serum CRP level. Reduced lung function is associated with increased levels of systemic inflammatory markers, which may have important pathophysiological and therapeutic implications for patients with stable COPD [28].

The presence of hyponatremia in COPD patients was another finding in our study. Patients with COPD are susceptible to hyponatremia for several reasons. A previous study found that activation of the renin-angiotensin-aldosterone system and abnormally elevated plasma arginine vasopressin levels in COPD may cause hyponatremia, mimicking the syndrome of inappropriate antidiuretic hormone secretion [29]. The systemic response to hypercapnia has the effect of reducing renal blood flow and, as a result, increasing water and sodium retention with the final effect of edema and hyponatremia. The

onset of edema is a poor prognostic factor [30].

The CAT consists of 8 items, each formatted as a semantic 6-point differential scale, which makes the tool easy for researchers to use and for patients to complete. The items related to cough and phlegm have greater discriminative power for milder disease, items concerning chest tightness and confidence leaving home have greater discriminative power for severe COPD, and the remaining items capture moderate health status impairment [10]. In our study, the mean CAT score was slightly higher in CVD patients with COPD (9.13±5.49) than in those without (7.57±3.83). Symptoms such as sputum production and cough were significantly more frequent in patients with COPD than in those without. In our study, 32 patients with COPD were assigned to group A or B, 16 in each group, and the severity of COPD was mild in most cases. Sputum production and cough are often ignored in CVD patients with early-stage COPD. Clinical physicians should arrange spirometry immediately to confirm the presence of COPD in patients who have much sputum production and cough. Early detection of COPD via spirometry in individuals with airway symptoms is not only practicable, but was able to identify a high proportion (34.8%) of individuals with airway obstruction in a previous study [31]. Early detection allows for early intervention to reduce the future burden of COPD and improve the prognosis, especially in patients with CVD.

We acknowledge some limitations in our prospective study design. First, only 166 patients were enrolled. Second, the enrolled patients were older than 40 years and had a history of smoking. Not all CAD patients are smokers, and further investigation is needed to confirm the prevalence of COPD among non-smokers. Third, echocardiography information was lacking. Patients might have additional dyspnea confounding factors such as sub-clinical left ventricle failure, left ventricle diastolic dysfunction or heart valve failures.

Conclusion

In the current study, prevalence of COPD in our outpatients with CAD was 19.3%. CAD patients older than 60 years with a history of smoking (>30 pack-years), a lower body weight (<60 kg), more sputum production (CAT score, sputum ≥1), and a lower serum sodium level (Na <135 mg/dl) were likely to have COPD. We have identified certain clues which may be helpful in the early detection of COPD in patients with CAD.

References

1. Bhatt SP, Dransfield MT. Chronic obstructive pulmonary disease and cardiovascular disease. Transl Res 2013; 162(4): 237-51.
2. Maclay JD, McAllister DA, Macnee W. Cardiovascular risk in chronic obstructive pulmonary disease. Respirology 2007; 12: 634-41.
3. Falk JA, Kadiev S, Criner GJ, *et al*. Cardiac disease in chronic obstructive pulmonary disease. Proc Am Thorac Soc 2008; 5: 543-8.
4. Sabit R, Bolton CE, Fraser AG, *et al*. Sub-clinical left and right ventricular dysfunction in patients with COPD. Respir Med 2010; 104(8): 1171-8.
5. Mills NL, Miller JJ, Anand A, *et al*. Increased arterial stiffness in patients with chronic obstructive pulmonary disease: a mechanism for increased cardiovascular risk. Thorax 2008; 63(4): 306-11.
6. Salisbury AC, Reid KJ, Spertus JA. Impact of chronic obstructive pulmonary disease on post-myocardial infarction outcomes. Am J Cardiol 2007; 99(5): 636-41.
7. Curkendall SM, DeLuise C, Jones JK, *et al*. Cardiovascular disease in patients with chronic obstructive

pulmonary disease, Saskatchewan Canada cardiovascular disease in COPD patients. Ann Epidemiol 2006; 16(1): 63-70.

8. Onishi K, Yoshimoto D, Hagan GW, *et al*. Prevalence of airflow limitation in outpatients with cardiovascular diseases in Japan. Int J Chron Obstruct Pulmon Dis 2014; 9: 563-8.
9. Soriano JB, Rigo F, Guerrero D, *et al*. High prevalence of undiagnosed airflow limitation in patients with cardiovascular disease. Chest 2010; 137(2): 333-40.
10. Jones PW, Harding G, Berry P, *et al*. Development and first validation of the COPD Assessment Test. Eur Respir J 2009; 34.3: 648-54.
11. Bestall J, Paul E, Garrod R, *et al*. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. Thorax 1999; 54.7: 581-6.
12. Vandevoorde J, Verbanck S, Schuermans D, *et al*. Obstructive and restrictive spirometric patterns: fixed cut-offs for FEV1/FEV6 and FEV6. Eur Respir J 2006; 27.2: 378-83.
13. Fletcher CM, Elmes PC, Fairbairn AS, *et al*. Significance of respiratory symptoms and the diagnosis of chronic bronchitis in a working population. Br Med J 1959; 2.5147: 257.
14. Vogelmeier CF, Criner GJ, Martinez FJ, *et al*. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report. GOLD executive summary. Am J Respir Crit Care Med 2017; 195.5: 557-82.
15. Kim S, Oh J, Kim YI, *et al*. Differences in classification of COPD group using COPD assessment test (CAT) or modified Medical Research Council (mMRC) dyspnea scores: a cross-sectional analyses. BMC Pulm Med 2013; 13:35.
16. Miller MR, Hankinson J, Brusasco V, *et al*. Standardisation of spirometry. Eur Respir J 2005; 26(2): 319-38.
17. Rabe KF, Hurd S, Anzueto A, *et al*. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 2007; 176(6): 532-55.
18. Ghoorah K, De Soyza A, Kunadian V. Increased cardiovascular risk in patients with chronic obstructive pulmonary disease and the potential mechanisms linking the two conditions: a review. Cardiol Rev 2013; 21(4): 196-202.
19. Iwamoto H, Yokoyama A, Kitahara Y, *et al*. Airflow limitation in smokers is associated with subclinical atherosclerosis. Am J Respir Crit Care Med 2009; 179(1): 35-40.
20. Sidney S, Sorel M, Quesenberry CP Jr, *et al*. COPD and incident cardiovascular disease hospitalizations and mortality: Kaiser Permanente Medical Care Program. Chest 2005; 128.4: 2068-75.
21. Luoto JA, Elmstahl S, Wollmer P, *et al*. Incidence of airflow limitation in subjects 65-100 years of age. Eur Respir J 2016; 47(2): 461-72.
22. Kojima S, Sakakibara H, Motani S, *et al*. Incidence of chronic obstructive pulmonary disease, and the relationship between age and smoking in a Japanese population. J Epidemiol 2007; 17: 54-60
23. Johannessen A, Omenaas E, Bakke P, *et al*. Incidence of GOLD-defined chronic obstructive pulmonary disease in a general adult population. Int J Tuberc Lung Dis 2005; 9: 926-32.
24. Chailleux E, Laaban JP, Veale D. Prognostic value of nutritional depletion in patients with COPD treated by long-term oxygen therapy: data from the ANTADIR observatory. Chest 2003; 123(6): 1460-6.
25. Marti S, Munoz X, Rios J, *et al*. Body weight and comorbidity predict mortality in COPD patients treated with oxygen therapy. Eur Respir J 2006; 27.4: 689-96.
26. Fimognari FL, Scarlata S, Conte ME, *et al*. Mechanisms of atherothrombosis in chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis 2008; 3.1: 89.
27. Sin DD. Why are patients with chronic obstructive pulmonary disease at increased risk of cardiovascular diseases? the potential role of systemic inflammation in chronic obstructive pulmonary disease. Circulation 2003; 107(11): 1514-9.
28. Gan WQ. Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and a meta-analysis. Thorax 2004; 59(7): 574-80.
29. de Leeuw PW, Dees A. Fluid homeostasis in chronic obstructive lung disease. Eur Respir J 2003;

22(Supplement 46): 33s-40s.

30. Valli G, Fedeli A, Antonucci R, *et al*. Water and sodium imbalance in COPD patients. Monaldi Arch Chest Dis 2004; 61: 112-16.

31. Ulrik CS, Lokke A, Dahl R, *et al*. Early detection of COPD in general practice. Int J Chron Obstruct Pulmon Dis 2011; 6:123-7.

Comparison of Outcomes with First- and Second-Generation Epidermal Growth Factor Receptor Inhibitors in Lung Adenocarcinoma Patients in Real-World Practice

Hsin-Wei Lin, Wen-Jui Wu, Chiate Yen, Yen-Ting Chen, Hsinpei Chung, Jian Su, Sheng-Hsiung Yang

Introduction: Tyrosine kinase inhibitors (TKIs) are the current standard first-line treatment for advanced lung adenocarcinoma harboring epidermal growth factor receptor (EGFR) mutations. In real-world practice, comparing the efficacy and toxicity of the 2 generations of TKIs is an important subject. The aim of this study, therefore, was to observe the clinical outcomes and adverse events of both first-generation and second-generation TKIs in real-world practice.

Methods: This study was conducted retrospectively using data collected at Mackay Memorial Hospital, Taipei, Taiwan, from January 1, 2013 to July 31, 2017. We analyzed progression-free survival (PFS) and overall survival (OS) to evaluate the effectiveness of first- and second-generation EGFR-TKIs in patients with EGFR mutations treated with first-line TKIs.

Results: A total of 176 patients were enrolled, including 138 patients in the first-generation TKI group (gefitinib and erlotinib) and 38 in the second-generation TKI group (afatinib). In the multivariate Cox proportional hazard model, second-generation TKIs had better PFS (hazard ratio (HR): 0.64, 95% confidence interval (CI): 0.42-0.97, p=0.036). However, OS was not statistically significantly different (HR: 0.66, 95% CI: 0.41-1.07, p=0.093). Furthermore, there was more folliculitis (second-generation TKI vs first-generation TKI: 68.4% vs. 47.6%, p=0.028), paronychia (60.5% vs. 16.1%, p<0.001), stomatitis (36.8% vs. 6.3%, p<0.001), and diarrhea (57.9% vs. 19.6%, p<0.001) of any grade in the second-generation TKI group.

Conclusion: The results of our study of real-world practice indicate that using second-generation TKIs yielded better PFS than first-generation TKIs at the cost of more side effects, especially folliculitis, paronychia, stomatitis and diarrhea. ***(Thorac Med 2020; 35: 64-74)***

Key words: lung adenocarcinoma, epidermal growth factor receptor, tyrosine kinase inhibitor

Division of Pulmonary and Critical Care Medicine, Mackay Memorial Hospital, Taipei, Taiwan
Hsin-Wei Lin and Wen-Jui Wu contributed equally to the manuscript.
Address reprint requests to: Dr. Sheng-Hsiung Yang, Division of Pulmonary and Critical Care Medicine, Mackay Memorial Hospital, #92 Chung-San North Road, Section 2, Taipei, Taiwan 10449, ROC

Introduction

Lung cancer is the most commonly occurring cancer and the leading cause of cancer deaths, including 2.1 million newly diagnosed patients and 1.8 million deaths in 2018 worldwide [1]. In recent years, the standard treatment has consisted of attempting to identify possible driver mutations and using appropriate targeted therapies [2]. The epidermal growth factor receptor (EGFR) mutation is the most common mutation in lung cancer patients, being noted in approximately 50% of Asian patients [3]. Female patients, non-smoking patients, and patients with a histology of adenocarcinoma have a higher incidence of EGFR mutations [4-5].

First-generation EGFR tyrosine kinase inhibitors (TKIs) such as gefitinib and erlotinib that reversibly block the HER-1 receptor have been proven to yield better outcomes than conventional chemotherapy [6-10]. Afatinib, a second-generation TKI, was designed to irreversibly block signaling from pan-HER receptors [11]. It has also shown better clinical outcomes than chemotherapy [12-13]. Few studies, however, have been designed to compare the clinical effects of first- and second-generation TKIs. The Lux-Lung 7 study found that afatinib was associated with longer progression-free survival (PFS) than gefitinib, but the difference between the 2 drugs with respect to overall survival (OS) was not significant [14-15]. A phase 3 trial of another second-generation TKI, dacomitinib, as first-line treatment and compared to gefitinib for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050) found a significant improvement in PFS and OS with the second-generation TKI [16-17]. However, the limitation of the ARCHER 1050 study was that patients with brain metastases were excluded. Gefitinib, erlotinib and afatinib are currently available as first-line therapies in Taiwan. The aim of this study was to observe the clinical outcomes and adverse events of both first-generation and second-generation TKIs in real-world practice.

Methods

Patients and clinical data

This study was conducted retrospectively using data collected at Mackay Memorial Hospital, Taipei, Taiwan, from January 1, 2013 to July 31, 2017. Data on all patients diagnosed with lung cancer were recorded in the lung cancer registry of our hospital. The medical records of these patients were reviewed. Patients with stage IV lung adenocarcinoma harboring sensitive EGFR mutations (including exon 19 deletion, exon 21 L858R, exon 18 G719X, exon 21 L861Q, and exon 20 S768I point mutations) were included in this study. Patients treated with an EGFR-TKI as first-line treatment were included. Exclusion criteria for the study were as follows: (1) An EGFR wild-type or EGFR exon 20 insertion-resistant mutation; (2) using an EGFR-TKI as first-line therapy <30 days; (3) having 2 active cancers; and (4) recurrent pulmonary adenocarcinoma after surgical resection of early-stage lung cancer.

The initial characteristics of the included patients, including age, gender, smoking status, performance status, metastatic sites, types of EGFR mutation, and type of TKI used (that is, first-generation or second-generation TKI), were analyzed.

Follow-up and assessments

Each patient was followed up at least every 3 months, with surveys including chest CT ex-

aminations with/without bone scan, brain imaging, or abdominal sonography. The PFS of each patient was defined as the period from the date of first TKI usage to the date of disease progression or death. OS was defined as the period from the date of first TKI usage to the date of death.

Statistical analysis

Patients were divided into 2 groups – a first-generation TKI group and a second-generation TKI group – based on the type of TKIs with which they were treated. The initial characteristics of the patients in the 2 groups were compared using the chi-square test or Fisher's exact test. The Welch t test was used for comparisons of continuous data. The Kaplan-Meier method and univariate and multivariate Cox proportional hazard models were used for analysis of PFS and OS. We selected variables that could confound survival, including age, gender, ECOG, smoking history, liver metastasis, bone metastasis and brain metastasis [18-22].

Results

Patient characteristics

A total of 491 patients with stage IV lung adenocarcinoma were included in the lung cancer registry of our hospital during the study period. Among these patients, 38 were without EGFR data and 176 had tumors not harboring an EGFR mutation that did not meet the inclusion criteria of the study. There were 277 patients with tumors harboring EGFR mutations, including 152 with an exon 19 deletion (54.9%), 130 with an exon 21 L858R point mutation (46.9%), 6 with an exon 18 G719X point mutation (2.2%), 4 with an exon 21 L861Q point mutation (1.4%), and 1 patient with an exon 20 S768I point mutation (0.4%). There was no patient with a de novo T790M mutation.

Ninety-six of the 277 patients were excluded (34 patients had incomplete data, 17 used a TKI for less than 30 days, 17 did not receive anti-cancer treatment, 19 did not receive a TKI as first-line therapy, 3 changed to another TKI without an obvious reason, and 6 had double cancers). In the end, 181 patients were enrolled into this study. There were also 5 patients who discontinued TKI therapy due to side effects, with 4 switching to another TKI and the other switching to chemotherapy. Because their therapies had changed, their PFS and OS outcomes could not be attributed to a particular TKI, so those 5 patients were excluded from the PFS and OS analysis and the comparison of patient characteristics. However, since they did experience adverse effects with their initial TKIs, they were included in the analysis of adverse effects (Figure 1).

Thus, a total 176 patients were included in the analysis of PFS and OS outcomes and the comparison of patient characteristics. There were 138 patients in the first-generation TKI group and 38 in the second-generation TKI group. Gender, smoking status, and the presence of liver, bone, and brain metastases were comparable between the 2 groups. Those patients using second-generation TKIs as first-line therapy were younger (age <65, second-generation TKI vs first-generation: 68.4% vs. 46.4%, p=0.018), and had a higher rate of exon 19 deletions (76.3% vs. 45.7%, P<0.001). The ECOG performance status of the 2 groups was not statistically significantly different (ECOG 0-1, second-generation TKI vs first-generation: 78.9% vs. 63.8%, p=0.083) (Table 1).

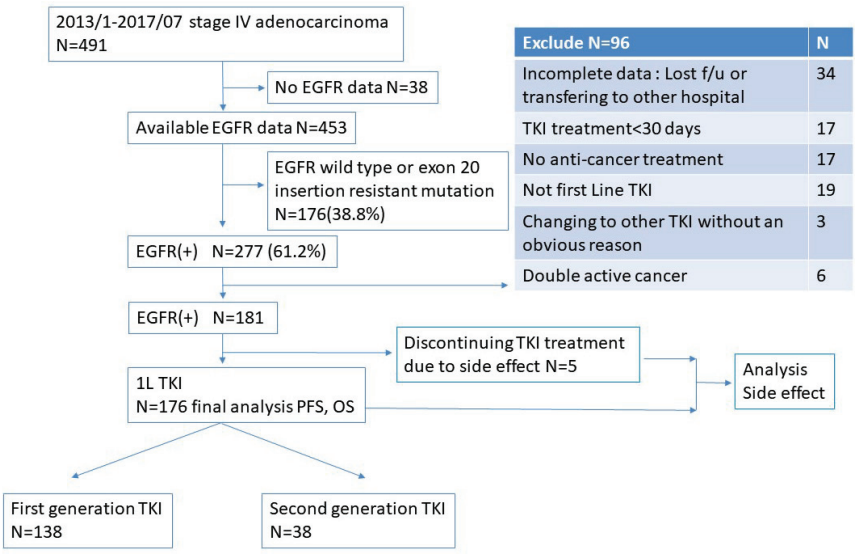


Fig. 1. Patient Selection Process

Table 1. Patient Characteristics

	First-generation TKI (n=138)	Second-generation TKI (n=38)	*p*
Age			0.018
<65 y/o	64 (46.4)	26 (68.4)	
≥65 y/o	74 (53.6)	12 (31.6)	
Gender, male (%)	51 (37.0)	13 (34.2)	0.850
Smoking*			0.290
Never	104 (77.6)	26 (68.4)	
Ever	30 (22.4)	12 (31.6)	
ECOG			0.083
0-1	88 (63.8)	30 (78.9)	
>1	50 (36.2)	8 (21.1)	
Liver metastasis	22 (15.9)	6 (15.8)	1.000
Bone metastasis	72 (52.2)	20 (52.6)	1.000
Brain metastasis	27 (19.6)	7 (18.4)	1.000
Exon 19 deletion**	63 (45.7)	29 (76.3)	0.0009
L858R**	79 (57.2)	9 (23.7)	0.0005
Pure rare mutation	4	1	

*4 patients had no records indicating their smoking history.

** 9 patients had both an exon 19 deletion and L858R mutations

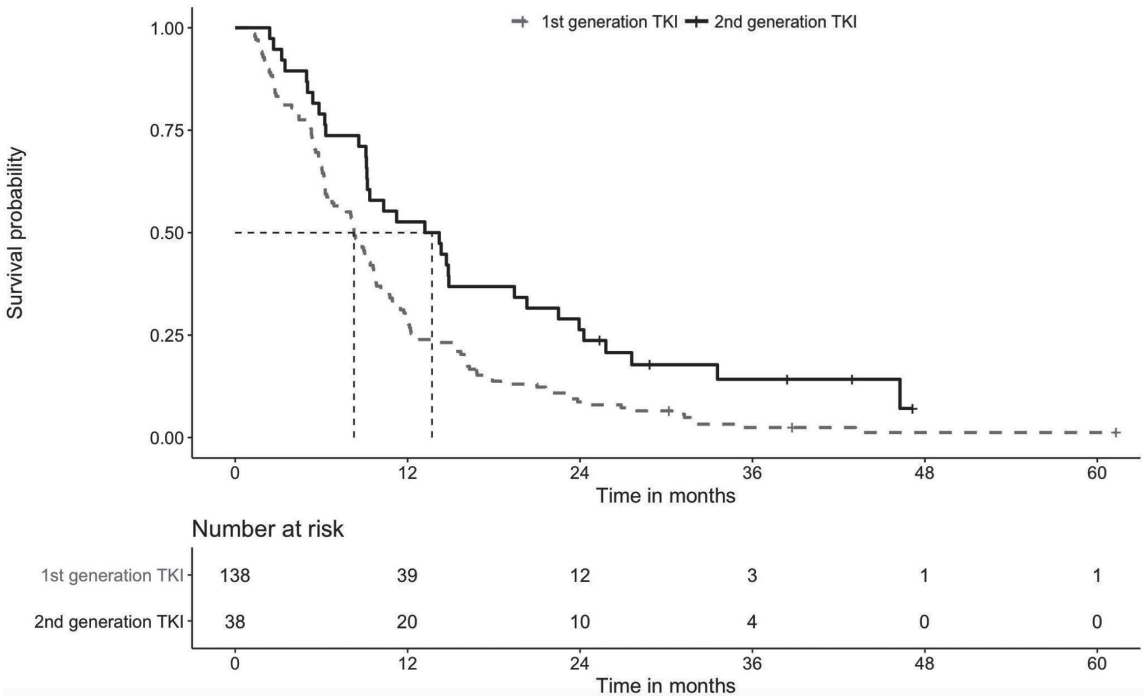


Fig. 2. KM Curves of Progression-Free Survival (PFS)
Median PFS (first-generation TKIs vs. second-generation TKIs): 8.27 months (95% CI: 6.70-960) vs. 13.70 months (95% CI: 9.13-19.4), p=0.002

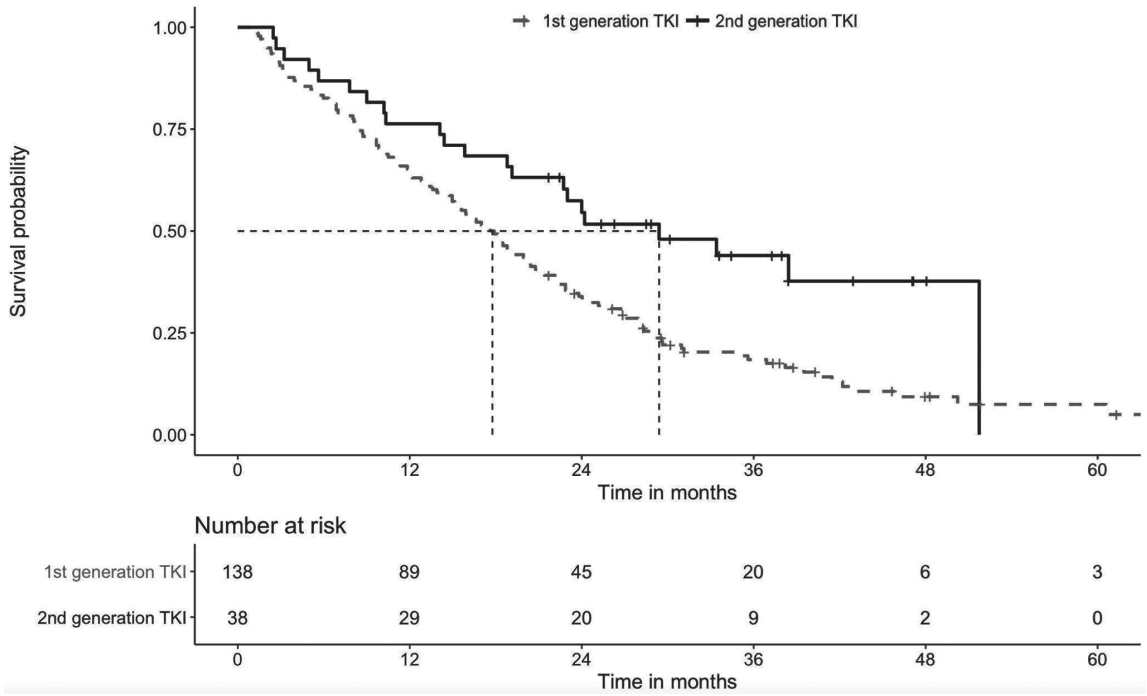


Fig. 3. KM Curves of Overall Survival (OS)
Median OS (first-generation TKIs vs. second-generation TKIs): 17.8 months (95% CI: 15.0-20.4) vs. 29.4 months (95% CI: 18.8-NA), p=0.004

Overall survival (OS) and progression-free survival (PFS)

Patients in the second-generation TKI group had better PFS (13.7 months vs. 8.27 months, p=0.002) and OS (29.4 months vs. 17.8 months, p=0.004) than those in the first-generation TKI group, according to Kaplan-Meier survival analysis (Figure 2 and Figure 3). In the multivariate Cox proportional hazard model, the second-generation TKI group had better PFS (hazard

Table 2. Univariate and Multivariate Cox Model Results for Progression-Free Survival

Predictors	Median PFS (months)	Univariate		Multivariate	
		HR (95% CI)	*p*	HR (95% CI)	*p*
Age					
≥65 y/o	8.32	1.25 (0.92-1.69)	0.156	1.26 (0.90-1.76)	0.175
<65 y/o	9.55				
Gender					
Female	9.67	0.82 (0.60-1.12)	0.209	0.93 (0.64-1.35)	0.710
Male	7.23				
ECOG					
0-1	9.78	0.66 (0.48-0.91)	0.011	0.70 (0.50-1.00)	0.049
>1	6.25				
Smoking					
Ever	8.18	1.39 (0.97-1.99)	0.069	1.42 (0.95-2.13)	0.085
Never	9.30				
Liver metastasis					
Yes	8.87	0.99 (0.65-1.50)	0.946	1.09 (0.70-1.70)	0.705
No	9.15				
Bone metastasis					
Yes	9.08	1.06 (0.78-1.43)	0.717	0.98 (0.70-1.36)	0.896
No	9.12				
Brain metastasis					
Yes	6.97	1.21 (0.82-1.78)	0.340	1.15 (0.76-1.73)	0.507
No	9.25				
EGFR					
Exon 19 deletion	9.57	0.70 (0.52-0.95)	0.022	0.77 (0.55-1.08)	0.124
Non-exon 19 deletion	8.32				
TKI					
Second-generation TKI	13.70	0.55 (0.38-0.81)	0.003	0.64 (0.42-0.97)	0.036
First-generation TKI	8.27				

Table 3. Univariate and Multivariate Cox Model Results for Overall Survival

Predictors	Median OS (months)	Univariate		Multivariate	
		HR (95% CI)	*p*	HR (95% CI)	*p*
Age					
≥65 y/o	15.9	1.45 (1.04-2.02)	0.028	1.37 (0.96-1.96)	0.081
<65 y/o	22.9				
Gender					
Female	22.2	0.71 (0.51-1.01)	0.055	0.71 (0.47-1.08)	0.110
Male	14.0				
ECOG					
0-1	22.7	0.59 (0.42-0.83)	0.003	0.70 (0.48-1.02)	0.064
>1	10.4				
Smoking					
Ever	14.0	1.32 (0.90-1.93)	0.157	1.23 (0.79-1.92)	0.357
Never	20.1				
Liver metastasis					
Yes	19.6	1.07 (0.69-1.66)	0.771	1.38 (0.86-2.20)	0.179
No	18.8				
Bone metastasis					
Yes	19.0	1.03 (0.74-1.43)	0.863	0.92 (0.64-1.31)	0.640
No	18.1				
Brain metastasis					
Yes	18.8	1.43 (0.95-2.16)	0.087	1.39 (0.91-2.13)	0.131
No	19.0				
EGFR					
Exon 19 deletion	23.0	0.56 (0.40-0.78)	<0.001	0.59 (0.40-0.85)	0.005
Non-exon 19 deletion	16.5				
TKI					
Second-generation TKI	29.4	0.52 (0.33-0.82)	0.005	0.66 (0.41-1.07)	0.093
First-generation TKI	17.8				

ratio (HR): 0.64, 95% confidence interval (CI): 0.42-0.97, p=0.036) (Table 2). However, OS in the multivariate Cox proportional hazard model was not statistically significantly different (HR: 0.66, 95% CI: 0.41-1.07, p=0.093) (Table 3). Better ECOG was significantly related to better PFS in both the univariate (HR: 0.66, 95% CI: 0.48-0.91, p=0.011) and multivariate (HR: 0.7, 95% CI: 0.50-1.00, p=0.049) models. In terms of OS, the presence of an exon 19 deletion was significantly related to better outcomes (HR: 0.59, 95% CI: 0.40-0.85, p=0.005).

Table 4. Toxicity Profiles of First- and Second-Generation TKIs

	Gr 1-2		Gr 3-4			Any grade		
	First-generation TKIs N=143	Second-generation TKIs N=38	First-generation TKIs N=143	Second-generation TKIs N=38	*P*	First-generation TKIs N=143	Second-generation TKIs N=38	*P*
Total	88 (61.5%)	32 (84.2%)	15 (10.5%)	7 (18.4%)	0.261	102 (71.3%)	32 (84.2%)	0.14
Folliculitis	64 (44.8%)	25 (65.8%)	4 (2.8%)	1 (2.6%)	1	68 (47.6%)	26 (68.4%)	0.028
Paronychia	22 (15.4%)	20 (52.6%)	1 (0.70%)	3 (7.9%)	0.030	23 (16.1%)	23 (60.5%)	<0.001
Stomatitis	9 (6.3%)	13 (34.2%)	0	1 (2.6%)	0.210	9 (6.3%)	14 (36.8%)	<0.001
Diarrhea	26 (18.2%)	19 (50%)	2 (1.40%)	3 (7.9%)	0.063	28 (19.6%)	22 (57.9%)	<0.001
Increased GOT/GPT	3 (2.1%)	0	6 (4.2%)	0	0.346	9 (6.3%)	0	0.208
Pneumonitis	0	0	2 (1.40%)	1 (2.6%)	0.509	2 (1.4%)	1 (2.6%)	0.509

Adverse effects

A total of 181 patients were included in the analysis of adverse effects (Table 4). Overall, the second-generation TKI group did not experience significantly higher toxicity (second-generation TKI vs first-generation: 84.2% vs. 74.3%, p=0.14). However, the second-generation TKI group did have higher rates of folliculitis (second-generation TKI vs first-generation TKI: 68.4% vs. 47.6%, p=0.028), paronychia (60.5% vs. 16.1%, p<0.001), stomatitis (36.8% vs. 6.3%, p<0.001), and diarrhea (57.9% vs. 19.6%, p<0.001) of any grade. Severe paronychia (second-generation TKI vs first-generation TKI: 7.9% vs. 0.7%, p=0.03), in particular, was also more prevalent in the second-generation TKI group. Meanwhile, liver function impairment was not a common adverse effect of the TKIs. More specifically, there was a greater but still limited rate of liver function impairment in the first-generation TKI group, but the difference between the 2 groups was not statistically significant (second-generation TKI vs first-generation TKI: 0% vs. 6.3%, p=0.208). Most of the cases of liver function impairment that did occur were severe, with 6 out of 9 cases (66.7%) involving grade 3-4 adverse effects. Half of these cases, that is, 3 patients with grade 3-4 liver function impairment, discontinued use of their the TKI. In total, 5 patients discontinued a TKI because of adverse effects: 3 of them discontinued their initial TKI due to severe liver function impairment, 1 due to severe diarrhea, and 1 due to severe pneumonitis. All 5 patients were treated with a first-generation TKI. There was no death caused by side effects of a TKI.

Discussion

Our study results indicate that the second-generation TKIs were superior to the first-generation TKIs in terms of PFS for lung adenocarcinoma patients with EGFR mutations. Despite the superior OS of second-generation TKIs compared to first-generation TKIs in the Kaplan-Meier analysis, the difference in OS between the 2 types of TKIs was not statistically significant in multivariate analysis. The results of our real-world practice study were similar to those of the LUX-Lung 7 study [14-15]. Other similar real-world studies have likewise showed consistent results [23-24].

Our study also showed that patients treated with second-generation TKIs were younger (aged ≥65 years, second-generation TKI vs first-generation TKI: 31.6% vs. 53.6%, p=0.018). These results were very similar to those of previous real-world studies [23-25]. These results suggest a younger patient treatment preference for second-generation TKIs, which may reflect a consideration of the toxicity of second-generation TKIs [24]. We also analyzed the side effects of both generations of TKIs, and found that any grade of folliculitis (second-generation TKI vs first-generation TKI: 68.4% vs. 47.6%, p=0.028), paronychia (60.5% vs. 16.1%, p<0.001), stomatitis (36.8% vs. 6.3%, p<0.001), and diarrhea (57.9% vs. 19.6%, p<0.001) were more common in the second-generation TKI group. More specifically, grade 3-4 paronychia (second-generation TKI vs first-generation TKI: 7.9% vs. 0.7%, p=0.03) was more prevalent in the second-generation TKI group. A study comparing the skin toxic effects associated with TKIs in lung cancer reported similar results [26]. They found that the most significant difference in adverse skin effects between the 2 generations of TKIs was that regarding paronychia. Meanwhile, despite the second-generation TKIs in that study contributing to a higher incidence of diarrhea, there was no significant difference in the rates of severe diarrhea between the 2 generations of TKIs, and no patients discontinued second-generation TKIs due to diarrhea. In the Lux-Lung 7 trial [14], the most frequently occurring grade 3 or worse adverse event was diarrhea (13%). The prevalence of severe diarrhea was lower (7.9%) in our study than in that clinical trial. The prevalence of severe diarrhea was lower still in the study conducted by Youjim Kim *et al*. (3%) [25], which was also a real-world study comparing the 2 generations of TKIs. The reasons why lower rates of adverse effects appear in real-word data may be that physicians have more experience with the management of adverse effects and that there are limitations to retrospective study designs that rely on medical records.

In the subgroup analysis of a prospective trial, longer OS with second-generation TKIs than with chemotherapy was noted in patients with an exon 19 deletion [27]. However, there have been no randomized controlled trials comparing the efficacy of first- and second-generation TKIs for patients with an exon 19 deletion. In our study, there were significantly more patients with an exon 19 deletion in the second-generation TKI group than in the first-generation group (76.3% vs. 45.7%, p<0.001), and in both this study and previous reports, an exon 19 deletion was a predictor of better outcomes [27-29]. Nevertheless, despite having more patients with an exon 19 deletion in the second-generation TKI group in this study, and after including the presence of an exon 19 deletion as a factor in the multivariate analysis, the use of second-generation TKIs remained a

significantly good prognostic factor for PFS.

There are several limitations to our study. First, the patients treated with second-generation TKIs were highly selected. This study was a retrospective study, and such biases may be present in such studies. Second, since patient data were collected from medical records, the incidence rates of side effects resulting from TKI usage may have been underestimated.

Conclusion

According to the real-world data of this study, the use of second-generation TKIs yielded better PFS than first-generation TKIs at the cost of more side effects, especially folliculitis, paronychia, stomatitis and diarrhea. Considering these side effects, the patients given second-generation TKIs as a first-line treatment in this study were highly selected. More specifically, they were younger and had a higher rate of exon 19 deletions.

References

1. Bray F, Ferlay J, Soerjomataram I, *et al*. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018; 68(6): 394-424.
2. Drilon A, Wang L, Arcila ME, *et al*. Broad, hybrid capture-based next-generation sequencing identifies actionable genomic alterations in lung adenocarcinomas otherwise negative for such alterations by other genomic testing approaches. Clin Cancer Res 2015; 21(16): 3631-9.
3. Chan BA, Hughes BG. Targeted therapy for non-small cell lung cancer: current standards and the promise of the future. Transl Lung Cancer Res 2015; 4(1): 36-54.
4. Marchetti A, Martella C, Felicioni L, *et al*. EGFR mutations in non-small-cell lung cancer: analysis of a large series of cases and development of a rapid and sensitive method for diagnostic screening with potential implications on pharmacologic treatment. J Clin Oncol 2005; 23(4): 857-65.
5. Kawaguchi T, Koh Y, Ando M, *et al*. Prospective analysis of oncogenic driver mutations and environmental factors: Japan molecular epidemiology for lung cancer study. J Clin Oncol 2016; 34(19): 2247-57.
6. Mok TS, Wu YL, Thongprasert S, *et al*. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009; 361(10): 947-57.
7. Maemondo M, Inoue A, Kobayashi K, *et al*. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med 2010; 362(25): 2380-8.
8. Mitsudomi T, Morita S, Yatabe Y, *et al*. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. Lancet Oncol 2010; 11(2): 121-8.
9. Zhou C, Wu YL, Chen G, *et al*. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. Lancet Oncol 2011; 12(8): 735-42.
10. Rosell R, Carcereny E, Gervais R, *et al*. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol 2012; 13(3): 239-46.
11. Li D, Ambrogio L, Shimamura T, *et al*. BIBW2992, an irreversible EGFR/HER2 inhibitor highly effective in preclinical lung cancer models. Oncogene 2008; 27(34): 4702-11.
12. Sequist LV, Yang JC, Yamamoto N, *et al*. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol 2013; 31(27): 3327-34.
13. Wu YL, Zhou C, Hu CP, *et al*. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. Lancet Oncol 2014; 15(2): 213-22.
14. Park K, Tan EH, O'Byrne K, *et al*. Afatinib versus

gefitinib as first-line treatment of patients with EGFR mutation-positive non-small-cell lung cancer (LUX-Lung 7): a phase 2B, open-label, randomised controlled trial. Lancet Oncol 2016; 17(5): 577-89.

15. Paz-Ares L, Tan EH, O'Byrne K, *et al*. Afatinib versus gefitinib in patients with EGFR mutation-positive advanced non-small-cell lung cancer: overall survival data from the phase IIb LUX-Lung 7 trial. Ann Oncol 2017; 28(2): 270-7.
16. Wu Y-L, Cheng Y, Zhou X, *et al*. Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, phase 3 trial. The Lancet Oncology 2017; 18(11):1454-66.
17. Mok TS, Cheng Y, Zhou X, *et al*. Improvement in overall survival in a randomized study that compared dacomitinib with gefitinib in patients with advanced non-small-cell lung cancer and EGFR-activating mutations. J Clin Oncol 2018; 36(22): 2244-50.
18. Visbal AL, Williams BA, Nichols FC, *et al*. Gender differences in non-small-cell lung cancer survival: an analysis of 4,618 patients diagnosed between 1997 and 2002. Ann Thorac Surg 2004; 78(1): 209-15; discussion 15.
19. Tsao AS, Liu D, Lee JJ, *et al*. Smoking affects treatment outcome in patients with advanced nonsmall cell lung cancer. Cancer 2006; 106(11): 2428-36.
20. Noronha V, Joshi A, Gokarn A, *et al*. The importance of brain metastasis in EGFR mutation positive NSCLC patients. Chemother Res Pract 2014; 2014: 856156.
21. Kuchuk M, Kuchuk I, Sabri E, *et al*. The incidence and clinical impact of bone metastases in non-small cell lung cancer. Lung Cancer 2015; 89(2): 197-202.
22. Wu KL, Tsai MJ, Yang CJ, *et al*. Liver metastasis predicts poorer prognosis in stage IV lung adenocarcinoma patients receiving first-line gefitinib. Lung Cancer 2015; 88(2): 187-94.
23. Tu CY, Chen CM, Liao WC, *et al*. Comparison of the effects of the three major tyrosine kinase inhibitors as first-line therapy for non-small-cell lung cancer harboring epidermal growth factor receptor mutations. Oncotarget 2018; 9(36): 24237-47.
24. Lau SC, Chooback N, Ho C, *et al*. Outcome differences between first- and second-generation EGFR inhibitors in advanced EGFR mutated NSCLC in a large population-based cohort. Clin Lung Cancer 2019; 20(5): e576-e83.
25. Kim Y, Lee SH, Ahn JS, *et al*. Efficacy and safety of afatinib for EGFR-mutant non-small cell lung cancer, compared with gefitinib or erlotinib. Cancer Res Treat 2019; 51(2): 502-9.
26. Chen KL, Lin CC, Cho YT, *et al*. Comparison of skin toxic effects associated with gefitinib, erlotinib, or afatinib treatment for non-small cell lung cancer. JAMA Dermatol 2016; 152(3): 340-2.
27. Yang JCH, Wu YL, Schuler M, *et al*. Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): analysis of overall survival data from two randomised, phase 3 trials. Lancet Oncol 2015; 16(2): 141-51.
28. Juan O, Popat S. Treatment choice in epidermal growth factor receptor mutation-positive non-small cell lung carcinoma: latest evidence and clinical implications. Ther Adv Med Oncol 2017; 9(3): 201-16.
29. Riely GJ, Pao W, Pham D, *et al*. Clinical course of patients with non-small cell lung cancer and epidermal growth factor receptor exon 19 and exon 21 mutations treated with gefitinib or erlotinib. Clin Cancer Res 2006; 12(3 Pt 1): 839-44.

Experience with Medical Thoracoscopy at a Single Institution

Ching-Kai Lin[1,2], Wei-Cheng Luo[3], Kai-Lun Yu[2], Lih-Yu Chang[2], Hung-Jen Fan[2,4], Yueh-Feng Wen[2], Chao-Chi Ho[1]

Introduction: Medical thoracoscopy (MT) is a minimally invasive procedure for inspection and biopsy of the pleural space and for therapeutic intervention. Here, we summarize our experience with MT at National Taiwan University Hospital, Hsin-Chu Branch.

Methods: A retrospective chart review of patients who underwent MT procedures for diagnostic or therapeutic purposes for various pleural diseases or undiagnostic pleural effusion from December 2015 to August 2018 was performed. Those without a definite diagnosis were excluded.

Results: Thirty-eight patients who underwent 40 MT procedures were enrolled in the present study. Twenty-one MT procedures were performed for diagnostic purposes, 5 for therapeutic purposes, and 14 for both diagnostic and therapeutic purposes during the same procedure. For the 35 diagnostic procedures, the overall diagnostic yield was 100%. Of the 19 procedures for therapeutic purposes, 18 were performed for adhesiolysis/fibrinolysis or decortication, and only 4 patients in this population required further treatment with surgical thoracoscopy. The remaining 1 patient had hepatic hydrothorax and underwent repair of a diaphragmatic defect.

Conclusion: MT is practical for both the diagnosis and treatment of various pleural diseases. ***(Thorac Med 2020; 35: 75-83)***

Key words: cryobiopsy, diaphragm repair, medical thoracoscopy, pleural disease, surgical thoracoscopy

Introduction

Medical thoracoscopy (MT) is a minimally invasive, endoscopic procedure for diagnosis of pleural diseases under conscious sedation and local anesthesia [1-2]. Pulmonologists can perform MT conveniently in a general bronchoscopy unit. Previous reports have indicated that for diagnosis of pleural effusion, MT has a much higher yield rate than thoracentesis, and a diagnostic accuracy similar to that of surgical thoracoscopy [3-4]. MT is now frequently used in many clinical institutions for the diagnosis of various pleural diseases.

[1]Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan; [2]Department of Internal Medicine, National Taiwan University Hospital, Hsin-Chu Branch, Hsinchu City, Taiwan; [3]Department of Surgery, National Taiwan University Hospital, Hsin-Chu Branch, Hsinchu City, Taiwan; [4]Department of Internal Medicine, National Taiwan University Hospital, Chu-Tung Branch, Hsinchu County, Taiwan
Ching-Kai Lin and Wei-Cheng Luo contributed equally to the manuscript.
Address reprint requests to: Dr. Yueh-Feng Wen, Department of Internal Medicine, National Taiwan University Hospital, Hsin-Chu Branch, No. 25, Lane 442, Sec. 1 Jingguo Rd., Hsinchu City 30059, Taiwan

In some circumstances, MT has also been applied for the treatment of pleural disease. For recurrent malignant pleural effusion and pneumothorax, chemical pleurodesis under MT has achieved a success rate of around 80% [5-7]. In cases with pleural infection, MT allows dissection of septations and adhesions, and facilitates accurate tube placement and drainage [8]. It reduces the need for surgical thoracoscopy, and thus the risk of operation and general anesthesia. However, MT has never been reported in the treatment of complex pleural conditions such as diaphragm repair. In this study, we summarize our experience with diagnostic and therapeutic MT at National Taiwan University Hospital, Hsin-Chu Branch. We also report a therapeutic MT procedure for diaphragm repair, and its outcome.

Methods

Subjects

The present study was based on a retrospective review of medical records. Data on patients who underwent MT procedures for diagnostic or therapeutic purposes at National Taiwan University Hospital, Hsin-Chu Branch, from December 2015 to August 2018 were gathered. Those without a definite diagnosis were excluded. Patient data on age, gender, indication, number of biopsies and procedure-related complications were documented. The maximal diameter of the specimen in the pathology report was also recorded. The study was approved by the Institutional Review Board (IRB #108-097-E) of National Taiwan University Hospital, Hsin-Chu Branch. Informed consent was waived as existing data were analyzed in a de-identified manner for this study.

Equipment and procedure for MT

All MT procedures were performed in an intensive care unit or a bronchoscopy room by pulmonologists or chest surgeons. All patients were placed in the lateral decubitus position, with the diseased side facing upward. Midazolam and fentanyl were administered intravenously before the procedure for conscious sedation. Chest ultrasonography was used to decide on a proper site to introduce the trocar. After local anesthesia with lidocaine, a 2-3 cm skin incision and blunt dissection with a Kelly clamp were performed, and then a dedicated trocar (MAJ-1058; Olympus Co., Tokyo, Japan) was introduced. A semi-rigid thoracoscopy (LTF-240; Olympus Co., Tokyo, Japan) was then inserted to the pleural cavity, followed by emptying of all fluid for the cell block and microbiologic study. After confirming the location of the pleural lesion, a 1.9-mm cryoprobe (ERBOKRYO CA, ERBE, Tuebingen, Germany) was used for specimen collection. If adhesion was noted during exploration of the pleural cavity, an alligator jaw grasping forceps (FG-47L-1; Olympus Co., Tokyo, Japan) was employed for adhesiolysis or fibrinolysis. If the alligator jaw grasping forceps failed in the therapeutic attempt, the trocar was replaced with an Alexis wound protector/retractor (C8313; Applied Medical, Rancho Santa Margarita, California), to create a larger entrance. A Kelly clamp was then inserted into the pleural space near our MT scope for mechanical adhesiolysis/fibrinolysis or decortication (Figure 1).

After completing the procedure, an 8-French pig-tail was inserted through the trocar or wound protector for air drainage. Then, the trocar or wound protector was removed. All biopsy specimens were placed in 10% formalin, embedded in paraffin and stained with hema-

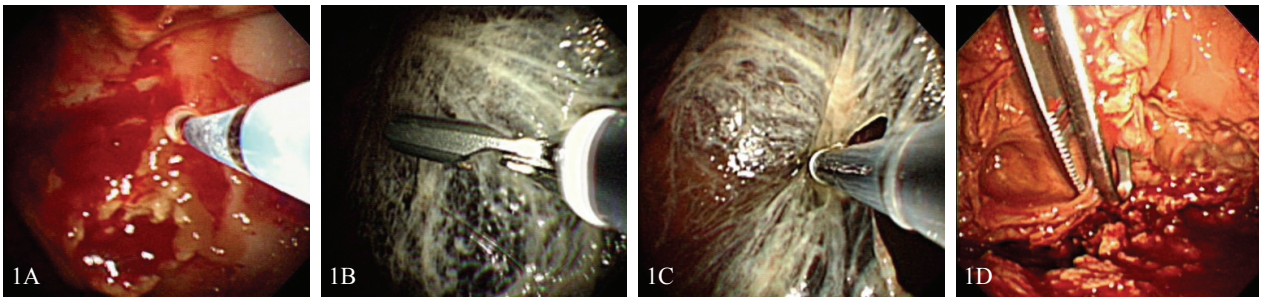


Fig. 1. Device used for medical thoracoscopy in diagnostic and therapeutic procedures. Panel A: 1.9-mm cryoprobe for pleural cryobiopsy. Panels B and C: Alligator jaw grasping forceps for adhesiolysis or fibrinolysis. Panel D: Kelly clamp for decortication.

toxylin and eosin for subsequent pathological analysis.

Statistical analysis

For diagnostic MT, accuracy was calculated via standard definitions. A "true-positive" result was defined as any MT samples that revealed a definite pathologic diagnosis (malignancy, microorganism or benign neoplasm) or microbiologic culture results. If the final diagnosis could not be made via microscopic or microbiologic studies, and no pleural lesion was found via MT, a "true-negative" result would still be considered when the pleural effusion subsided through specific management (antibiotics, diuretics, or hemodialysis), as detected by computed tomography imaging follow-up within 3 months.

Improvement in the patient's clinical condition (including dyspnea, fever curve, oxygen demand, etc.) or laboratory data (such as white blood cell count, inflammatory markers, chest images, etc.) after the MT procedure was considered a good therapeutic outcome. No improvement in the patient's clinical condition and laboratory data or the need for further surgical intervention after MT was regarded as a poor therapeutic outcome.

Results

Patients and MT procedures

A total of 39 patients underwent MT procedures during the study period. In the end, 38 patients who underwent 40 MT procedures were enrolled in the present study. One patient was excluded because of a lack of a definite diagnosis. Twenty-nine patients were males and 9 were females. The mean age was 66.4 years. Among the 40 MT procedures, 21 were performed for diagnosis, 5 for therapeutic MT, and 14 for both diagnostic and therapeutic purposes. One patient developed hypotension and bradycardia during the procedure. After the procedure, 1 patient developed lung atelectasis, 1 had subcutaneous emphysema, and 2 eventually expired due to causes that were not procedure-related (Figure 2, Table 1).

Results of diagnostic MT

Among the 35 procedures that were performed for diagnosis alone or for both therapeutic and diagnostic purposes, the mean number of biopsies was 5.8 and the mean sample size was 1.8 cm. Seven patients were diagnosed with malignancy: 2 with pulmonary adenocarcinoma, 1 with breast cancer, 1 with nasopharyngeal carcinoma, 1 with lymphoma, 1 with malignant

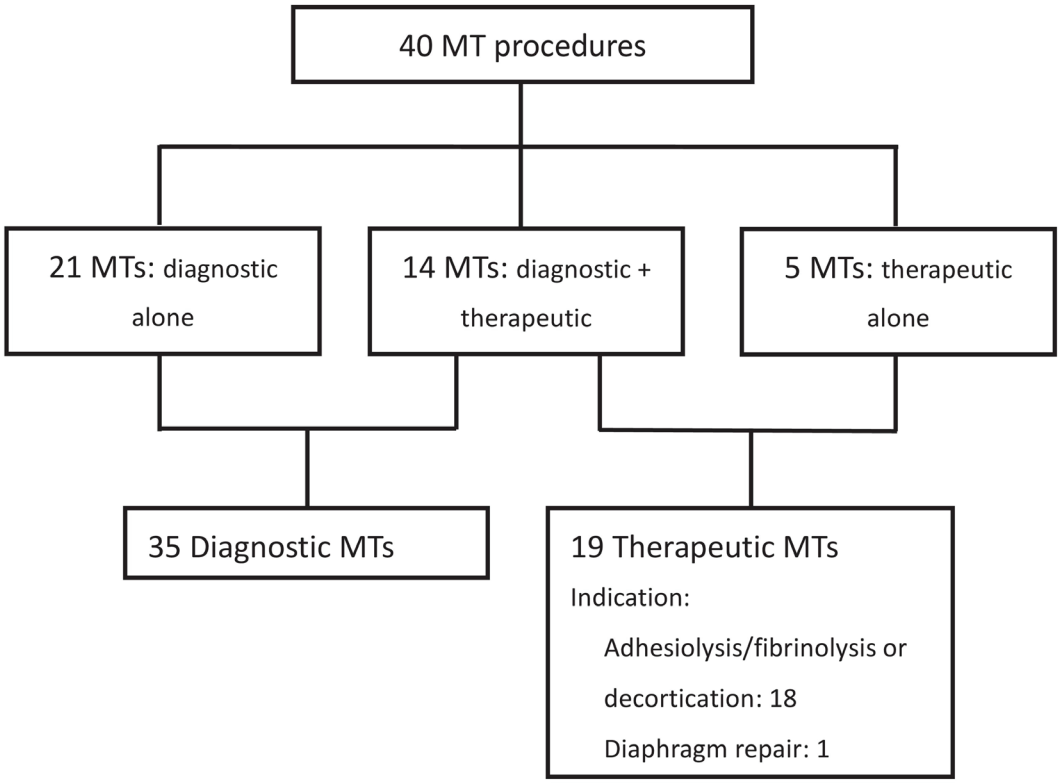


Fig. 2. Classification of the 40 MT procedures. A total of 35 procedures were performed for diagnostic purposes, among which 21 were for diagnosis alone and 14 for both diagnostic and therapeutic purposes. Nineteen procedures were performed for therapeutic purposes or for both diagnostic and therapeutic needs. MT: medical thoracoscopy.

Table 1. Baseline Characteristics of the Study Patients and the Procedures

Characteristics	N
Patients	38
Age (years-old, range)	66.4 (26-97)
Male gender (%)	29 (76.3 %)
MT procedure	40
Indication (%):	
Diagnostic	21 (52.5)
Therapeutic	5 (12.5)
Diagnostic + Therapeutic	14 (35)
Complication: (%)	5 (12.5)
Hypotension bradycardia	1 (2.5)
Lung atelectasis	1 (2.5)
Subcutaneous emphysema	1 (2.5)
Expired	2 (5)
Sepsis (D16)	1 (2.5)
Respiratory failure (D41)	1 (2.5)

D = day; MT = medical thoracoscopy; N = number

mesothelioma, and 1 with alveolar soft part sarcoma. Twenty-eight patients were finally diagnosed with non-malignant etiologies: 9 with empyema, 8 with tuberculous pleurisy, 1 with a benign adipose tumor, 1 with a solitary fibrous tumor, 1 with hepatic hydrothorax, 4 with post-infection pleural adhesion, and 4 were negative for pleural abnormality. For the 4 patients with pleural effusion and a negative pleural finding, 1 was speculated to have a uremic symptom, 1 had poor postoperative lymphatic drainage, and the other 2 had fluid overload. These 4 patients were successfully treated with more aggressive diuretics or renal replacement therapy. The overall diagnostic yield of MT in this study was 100% (Figure 2, Table 2).

Table 2. Baseline Characteristics of Diagnostic MT (N = 35)

Procedure Characteristics	N
Biopsy times (range)	5.8 (1-10)
Sample size (cm, range)	1.8 (0.2-8.1)
Final diagnosis (%)	
Malignancy	7 (20)
Lung adenocarcinoma	2 (5.7)
Breast cancer	1 (2.9)
Nasopharyngeal carcinoma	1 (2.9)
Lymphoma	1 (2.9)
Malignant mesothelioma	1 (2.9)
Alveolar soft part sarcoma	1 (2.9)
Non-malignancy	28 (80)
Empyema	9 (25.7)
Tuberculous pleurisy	8 (22.9)
Benign adipose tumor	1 (2.9)
Solitary fibrous tumor	1 (2.9)
Hepatic hydropneumothorax	1 (2.9)
Adhesion	4 (11.4)
Negative	4 (11.4)
End-stage renal disease	1 (2.9)
Post-operation-related poor lymphatic drainage	1 (2.9)
Fluid overload	2 (5.7)
Diagnostic accuracy (%)	35 (100)

MT = medical thoracoscopy; N = number

Results of therapeutic MT

In the present study, 17 patients underwent 19 MT procedures for therapeutic purposes or for both diagnostic and therapeutic needs (Figure 2, Table 3). Two patients underwent therapeutic MT twice, 1 for malignant pleural effusion and the other for empyema. Most MT procedures (18/19, 94.7%) were performed for adhesiolysis/fibrinolysis or decortication in patients with malignant pleural effusion, empyema, tuberculous pleurisy or post-infection pleural adhesion. The adhesiolysis failed in 4 patients with empyema in this study because even the Kelly clamp could not break the very tight adhesion between the parietal and visceral pleura. Therefore, further surgical thoracoscopy was required.

Hepatic hydrothorax due to a diaphragmatic defect was confirmed with MT in 1 patient. Therefore, diaphragm repair was performed during the same procedure (Figure 3). During the procedure, a round-shaped defect was detected at the dome of the diaphragm. Bio-glue was sprayed over the defect, and then a mesh was used to cover the whole diaphragm using the Kelly clamp. The amount of pleural effusion drainage started decreasing on day 2 of the diaphragm repair. One week after the procedure, the drainage amount decreased to less than 200 milliliters a day. On day 16 after the procedure, the patient died due to a new *Klebsiella pneu-*

Table 3. Baseline Characteristics of Therapeutic MT

Characteristics	N
Patients	17
Procedure number	19
Final diagnosis (%)	
Malignant PLE	3 (15.8)
Empyema	9 (47.4)
TB pleurisy	2 (10.5)
Pleura adhesion	4 (21.1)
Hepatic hydrothorax	1 (5.3)
Procedure (%)	
Decortication	7 (36.8)
Adhesiolysis/fibrinolysis	11 (57.9)
Diaphragm repair	1 (5.3)
Further VATS (%)	4 (21.1)
Complication (%):	4 (21.1)
Subcutaneous emphysema	1 (5.3)
Hypotension bradycardia	1 (5.3)
Sepsis (D16)	1 (5.3)
Respiratory failure (D41)	1 (5.3)

D = day; MT = medical thoracoscopy; N = number; PLE = pleural effusion; VATS = video-assisted thoracoscopic surgery

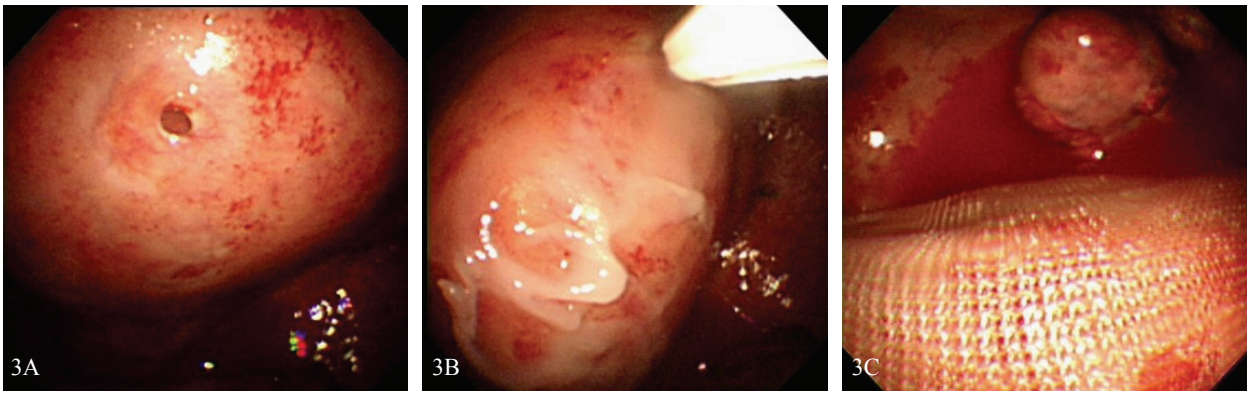


Fig. 3. Procedure for diaphragm repair via medical thoracoscopy. Panel A: A round-shaped defect detected at the dome of the diaphragm. Panel B: Bio-glue sprayed over the defect. Panel C: A mesh covered the whole diaphragm.

moniae bacteremia with septic shock. During the period of the bacteremia, analysis of pleural effusion showed a transudate, so procedure-related infection was unlikely.

Discussion

This retrospective study revealed that MT had a high degree of accuracy for the diagno-

sis of various pleural diseases. For therapeutic purposes, MT procedures also had a high level of efficacy. The usage of surgical thoracoscopy could be minimized if an MT procedure was performed initially.

Pleural effusion and subpleural lesions are the most common manifestations of pleural disease [9]. These clinical findings can be easily detected by ultrasonography. Ultrasound-guided procedures are the first choice for the diagnosis of pleural diseases because of the low cost and availability in general wards. However, even when combining thoracentesis and a core needle biopsy, the diagnostic yield is only 60-70% for both tuberculous pleurisy and malignant pleural effusion [3]. In our study population, the 8 patients with tuberculous pleurisy received thoracentesis for pleural effusion analysis at least twice and core needle biopsy once initially, but still lacked a definite diagnosis. A more advanced procedure to further increase the diagnostic accuracy of various pleural diseases is required.

MT is a minimally invasive procedure for inspection and biopsy of the pleural space [2]. Previous publications revealed that the diagnostic yield of MT was more than 90% [7,10]. Diagnostic accuracy in the present study was 100%, even higher than in previous studies. Compared to forceps biopsy results in other reports, the use of the cryoprobe for pleural biopsy may explain the higher diagnostic accuracy in the present study. Tousheed *et al*. reported that the sizes of specimens obtained with a cryoprobe were significant larger than those with conventional forceps [11]. The histopathologic analysis also revealed better quality specimens with cryobiopsy. Chen *et al*. reported a similar result [12]. The mean size of specimens obtained via a cryoprobe in our study was 1.8 cm, which was larger than those (<1 cm) obtained via forceps biopsy in the previous 2 studies [11-12]. Some studies claimed that the sample obtained with MT was too small to reach a diagnosis of mesothelioma [13-14]. In the present study, some uncommon etiologies such as malignant mesothelioma or alveolar soft part sarcoma could be diagnosed with cryobiopsy via MT. Nakai *et al*. also showed that cryobiopsy via MT had a higher diagnostic rate for malignant mesothelioma than the conventional biopsy technique [15]. Our findings offered evidence that cryobiopsy performed via MT had high diagnostic accuracy for a broad spectrum of pleural diseases.

The role of therapeutic MT has been reported. Talc pleurodesis via MT could be performed in cases of malignant pleural effusion and pneumothorax [5,7]. At the early stage of empyema, mechanical adhesiolysis via MT may be used as a first-line treatment without delay for patients who have had septations [8]. However, surgical thoracoscopy is still required for late-stage empyema with severe pleural adhesions. At this stage, patients usually have poor lung functioning or a poor performance status [10]. In the present study, 9 patients with empyema were in a late stage with severe pleural adhesions. Only 4 patients needed surgical thoracoscopy following MT. Other patients with malignant pleural effusion, tuberculous pleurisy or post-infection pleural adhesions also received adhesiolysis/fibrinolysis or decortication during the MT procedure. None of them required further surgical intervention. For difficult cases, an improved outcome of adhesiolysis/fibrinolysis or decortication via MT might be attributed to the utilization of large-size instruments. The diameter of the working channel used in MT was larger than that of the conventional bronchoscope.

Therefore, a larger instrument routinely used in gastrointestinal endoscopy, such as an alligator jaw grasping forceps, could pass through the working channel of MT. The dedicated trocar was replaced with an Alexis wound protector/retractor, which could create a larger tunnel from the skin to the pleural cavity and allow the use of large surgical instruments for more advanced procedures. Hence more complicated procedures could still be attempted via MT.

MT can minimize the use of surgical thoracoscopy, and avoid the risk of general anesthesia [16]. Only a single port of entry into the thoracic cavity is required, as compared with 3 ports in surgical thoracoscopy [10], and there are fewer reported complications with MT procedures. In the present study, we reported what we believe, to the best of our knowledge, is the first case in which a diaphragm defect was repaired via a MT procedure. The amount of pleural effusion drainage in the patient gradually decreased after our MT procedure. However, the patient died on the 16th day after the procedure, so the long-term benefits are uncertain.

In previous reports, complications with MT were rare [17-19]. Most of the study populations in the literature received diagnostic MT. However, the complication rate in our study was higher (5/40, 12.5%); most of the adverse events (4/5, 80%) occurred during therapeutic MT procedures. Two patients died after the MT procedures. One patient with hepatic hydrothorax underwent diaphragm repair and died from *Klebsiella pneumoniae* bacteremia with septic shock on the day 16 after the procedure. Multiple analyses of the pleural effusion all revealed transudate and negative culture results. Another patient had left-side empyema and received MT for decortication. New right-side nosocomial pneumonia complicating acute respiratory distress syndrome developed 1 month after the MT. The patient died on day 41. We believe that the performance status of these 2 patients was worse. MT seemed not to be the cause of their deaths in the present study.

Our study has several limitations. First, there was a relatively small number of patients in this study. Second, the study was performed retrospectively. Some clinical information was not recorded, such as procedure time and some minor adverse events (wound pain, wound oozing). A prospective study is warranted to further evaluate our findings.

Conclusion

This study showed that MT is a useful procedure for both the diagnosis and treatment of various pleural diseases. High diagnostic accuracy can be achieved when combining MT with cryobiopsy. MT can minimize the usage of surgical thoracoscopy, and therefore decrease the complications of that procedure.

References

1. Lee P, Mathur PN, Colt HG. Advances in thoracoscopy: 100 years since Jacobaeus. Respiration 2010; 79: 177-86.
2. Michaud G, Berkowitz DM, Ernst A. Pleuroscopy for diagnosis and therapy for pleural effusions. Chest 2010; 138: 1242-6.
3. Loddenkemper R, Mathur PN, Lee P, *et al*. History and clinical use of thoracoscopy/pleuroscopy in respiratory medicine. Breathe 2011; 8: 145-55.
4. Rozman A, Camlek L, Marc-Malovrh M, *et al*. Rigid versus semi-rigid thoracoscopy for the diagnosis of pleural disease: a randomized pilot study. Respirology 2013; 18: 704-10.
5. Leemans J, Dooms C, Ninane V *et al*. Success rate of medical thoracoscopy and talc pleurodesis in malignant pleurisy: A single-centre experience. Respirology 2018;

23: 613-7.
6. Wrightson JM, Helm EJ, Rahman NM, *et al*. Pleural procedures and pleuroscopy. Respirology 2009; 14: 796-807.
7. Weissberg D, Kaufmann M. Diagnostic and therapeutic pleuroscopy. Experience with 127 patients. Chest 1980; 78: 732-5.
8. Brutsche MH, Tassi GF, Györik S, *et al*. Treatment of sonographically stratified multiloculated thoracic empyema by medical thoracoscopy. Chest 2005; 128: 3303-9.
9. Akulian J, Feller-Kopman D. The past, current and future of diagnosis and management of pleural disease. J Thorac Dis 2015; 7: S329-38.
10. Kim SJ, Choi SM, Lee J, *et al*. Medical thoracoscopy in pleural disease: experience from a one-center study. Tuberc Respir Dis 2017; 80: 194-200.
11. Tousheed SZ, Manjunath PH, Chandrasekar S, *et al*. Cryobiopsy of the pleura: an improved diagnostic tool. J Bronchology Interv Pulmonol 2018; 25: 37-41.
12. Chen CH, Cheng WC, Wu BR, *et al*. Feasibility and safety of pleuroscopic cryobiopsy of the pleura: a prospective study. Can Respir J 2018; 2018: 6746470.
13. Greillier L, Cavailles A, Fraticelli A, *et al*. Accuracy of pleural biopsy using thoracoscopy for the diagnosis of histologic subtype in patients with malignant pleural mesothelioma. Cancer 2007; 110: 2248-52.
14. Sasada S, Kawahara K, Kusunoki Y, *et al*. A new electrocautery pleural biopsy technique using an insulated-tip diathermic knife during semirigid pleuroscopy. Surg Endosc 2009; 23: 1901-7.
15. Nakai T, Matsumoto Y, Sasada S, *et al*. Cryobiopsy during flex-rigid pleuroscopy: an emerging alternative biopsy method in malignant pleural mesothelioma. A comparative study of pathology. Jpn J Clin Oncol 2019; 49: 559-66.
16. Shojaee S, Lee HJ. Thoracoscopy: medical versus surgical in the management of pleural diseases. J Thorac Dis 2015; 7: S339-51.
17. Lee P, Colt HG. Rigid and semirigid pleuroscopy: the future is bright. Respirology 2005; 10: 418-25.
18. Ernst A, Hersh CP, Herth F, *et al*. A novel instrument for the evaluation of the pleural space: an experience in 34 patients. Chest 2002; 122: 1530-4.
19. McLean AN, Bicknell SR, McAlpine LG, *et al*. Investigation of pleural effusion: an evaluation of the new Olympus LTF semiflexible thoracofiberscope and comparison with Abram's needle biopsy. Chest 1998; 114: 150-3.

Osimertinib Combined with Cetuximab for T790M and C797S Mutation in Non-small Cell Lung Cancer - Case Series

Chia-Ling Chang, Jin-Yuan Shih

Osimertinib, a third generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, is proven to be effective in managing T790M mutation in non-small cell lung cancer (NSCLC). However, osimertinib becomes resistant when both T790M and C797S mutations are present. Our goal was to evaluate the treatment response of T790M and C797S-positive NSCLC treated with osimertinib and cetuximab. A retrospective chart review of EGFR T790M and C797S mutations positive NSCLC patients, treated with osimertinib and cetuximab at National Taiwan University Hospital, from July 2017 to October 2018 was performed. Four patients with NSCLC carried EGFR T790M and C797S mutations. They were all treated with osimertinib and cetuximab. Progression-free survival of these patients was 6.7, 4.9, 4.1 and 1 month, respectively. Osimertinib, combined with cetuximab seems to be beneficial for NSCLC patients with acquired T790M and C797S positive NSCLC. Further studies are necessary in order to understand the mechanism. ***(Thorac Med 2020; 35: 84-90)***

Key words: osimertinib, cetuximab, T790M and C797S mutations, non-small cell lung cancer

Introduction

Lung cancer is the second most common cancer and accounted for about 14% of all newly-diagnosed cancer cases in the United States in 2018. It remains the leading cause of cancer-related mortality. The 5-year survival rate for stage IVA and IVB non-small cell lung cancer (NSCLC) is 10% and 1%, respectively [1]. Choosing the best therapeutic strategy for advanced NSCLC may depend on the presence of an epidermal growth factor receptor (EGFR) mutation, which can be treated with an EGFR tyrosine kinase inhibitor (TKI) [2]. The prevalence of EGFR mutations in Asia (38.4%) was higher than that in North and South America (24.4%) and Europe (14.1%) [3]. Exon 19 deletions and exon 21 L858R mutations are the most common EGFR mutations in advanced NSCLC [4]. EGFR mutation-positive NSCLC can be treated with first, second or third generation EGFR TKIs according to the National Comprehensive Cancer Network (NCCN) guideline. If disease progression of EGFR

Division of Pulmonary Medicine, Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan.
Address reprint requests to: Dr. Jin-Yuan Shih, Division of Pulmonary Medicine, Department of Internal Medicine, National Taiwan University Hospital, No. 7, Chung-Shan South Road, Taipei 100, Taiwan

mutation-positive NSCLC under treatment with a first or second-generation EGFR TKI, is detected, T790M mutation testing is suggested in the NCCN guideline [5].

Osimertinib, a third-generation EGFR TKI, is proven to be effective in managing T790M mutations in NSCLC [6]. Median progression-free survival (PFS) of NSCLC patients with an EGFR T790M mutation treated with osimertinib was 10.1 months [7]. The C797S mutation is the most well-known cause of osimertinib resistance [8]. This EGFR mutation disturbs the covalent binding between osimertinib and its receptor, consequently reducing the efficacy of osimertinib [2]. Combination therapy with third- and first-generation TKIs is effective against T790M and trans-C797S mutations, but not cis-C797S mutations [9]. A previous animal study indicated that the combination of osimertinib plus cetuximab increased the efficacy of osimertinib as second-line therapy for osimertinib-resistant NSCLC in mice. The treatment response rate was 50~66.6%, and no significant toxicities were found [10]. Our goal in this study was to evaluate the treatment response of T790M and C797S-positive NSCLC to combined osimertinib and cetuximab, regardless of their isomeric type.

Methods

A retrospective chart review of EGFR T790M and C797S mutation-positive NSCLC patients, treated with osimertinib and cetuximab at National Taiwan University Hospital in northern Taiwan, from July 2017 to October 2018, was performed.

EGFR T790M mutation-positive lung adenocarcinoma patients under osimertinib treatment and suffering from progressive disease due to EGFR C797S mutations were identified. The subsequent therapeutic strategy chosen to treat these patients was to combine osimertinib 80 mg daily with biweekly cetuximab 200~250 mg/m^2 until further disease progression was detected. Disease status was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 [11]. PFS was set as the endpoint.

Results

Four patients with NSCLC carried EGFR T790M and C797S mutations (Table 1). Rebiopsy was performed when disease progression occurred. Osimertinib and cetuximab were administrated when both T790M and C797S mutations were detected.

Case 1: The patient was a 66-year-old woman diagnosed with stage IV lung adenocarcinoma. Her tumor had an EGFR mutation of an exon 19 deletion plus de novo T790M. Erlotinib, nazartinib and osimertinib were sequentially prescribed based on the EGFR mutation. A C797S mutation was detected by liver biopsy after the patient had taken osimertinib for 11.6 months. The next regimen was osimertinib 80 mg daily plus cetuximab 200mg/m^2 every 2 weeks. The patient then had RECIST-evaluated stable disease (SD) for 6.7 months before lung metastases increased in size and number and a new satellite liver metastasis was found (Table 1 and Figure 1).

Case 2: The patient was an 85-year-old man initially with EGFR exon 21 L858R mutation-positive NSCLC. He had used erlotinib, gefitinib, and osimertinib sequentially based on the EGFR mutation. He developed progressive disease after 14.7 months of osimertinib use. EGFR T790M and C797S mutations were

Table 1. Osimertinib and Cetuximab for Stage IV Lung Adenocarcinoma with EGFR T790M and C797S Mutations

Case	1	2	3	4
Age/Gender	66/Female	85/Male	64/Female	61/Female
Initial EGFR mutation	Exon 19 deletion and T790M	L858R	Exon 19 deletion	L858R
Prior TKI use	Erlotinib Nazartinib Osimertinb	Erlotinib Gefitinib Osimertinib	Erlotinib Afatinib Osmertinib	Gefitinib Erlotinib Osimertinib
Length of time before C797S mutation detection after osimertinib	11.6 months	14.7 months	7.7 months	4.8 months
Line of osimertinib and cetuximab	10^{th} (2018/01/23)	8^{th} (2018/02/02)	13^{th} (2017/11/03)	15^{th} (2018/03/23)
Progression-free survival	6.7 months	4.9 months	4.1 months	1 month

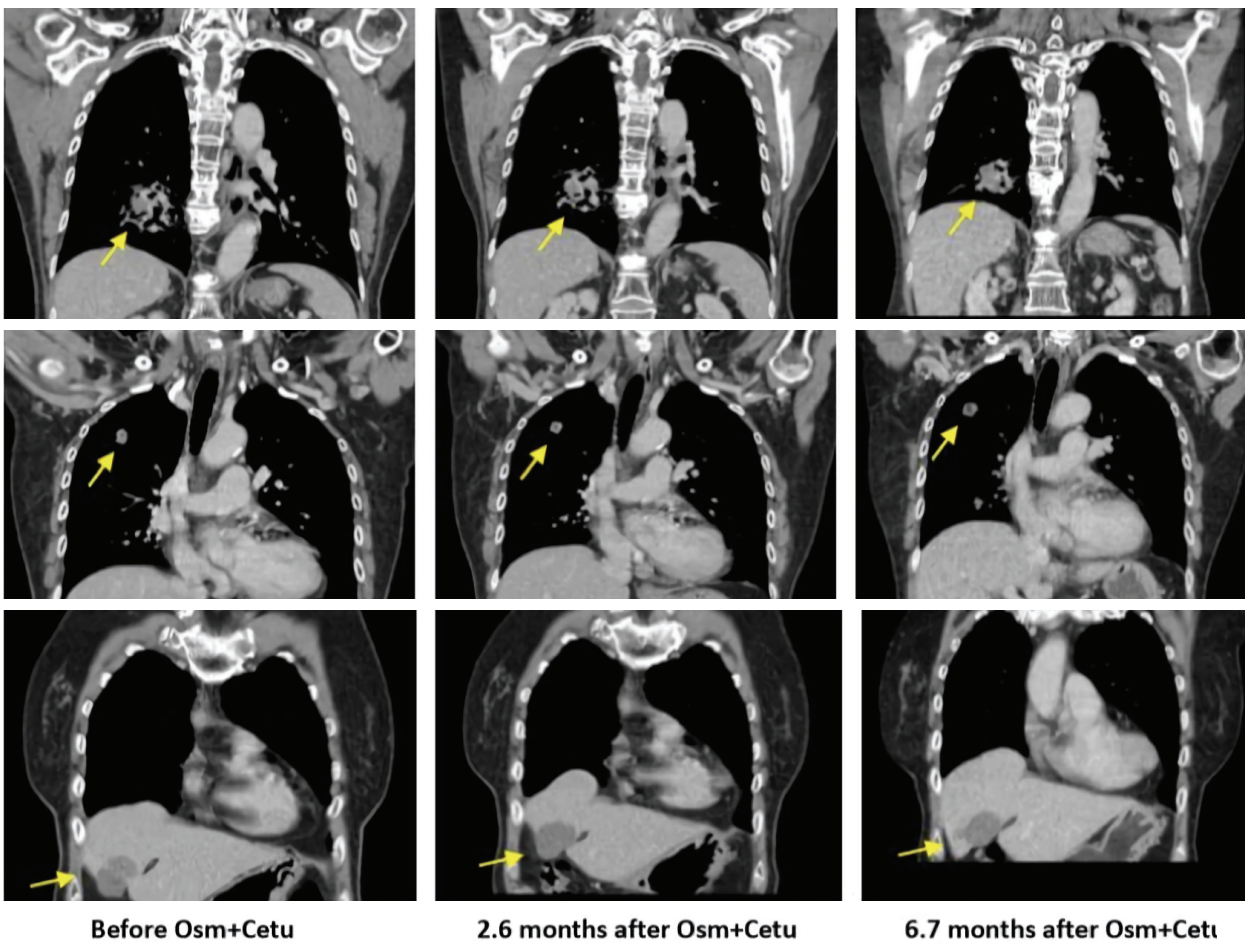


Fig. 1. Case 1: The patient was diagnosed with stage IV lung adenocarcinoma with EGFR T790M and C797S mutations. Osimertinib 80 mg daily plus cetuximab 200 mg/m^2 biweekly were prescribed. PFS was 6.7 months. (Osm: Osimertinib; Cetu: Cetuximab)

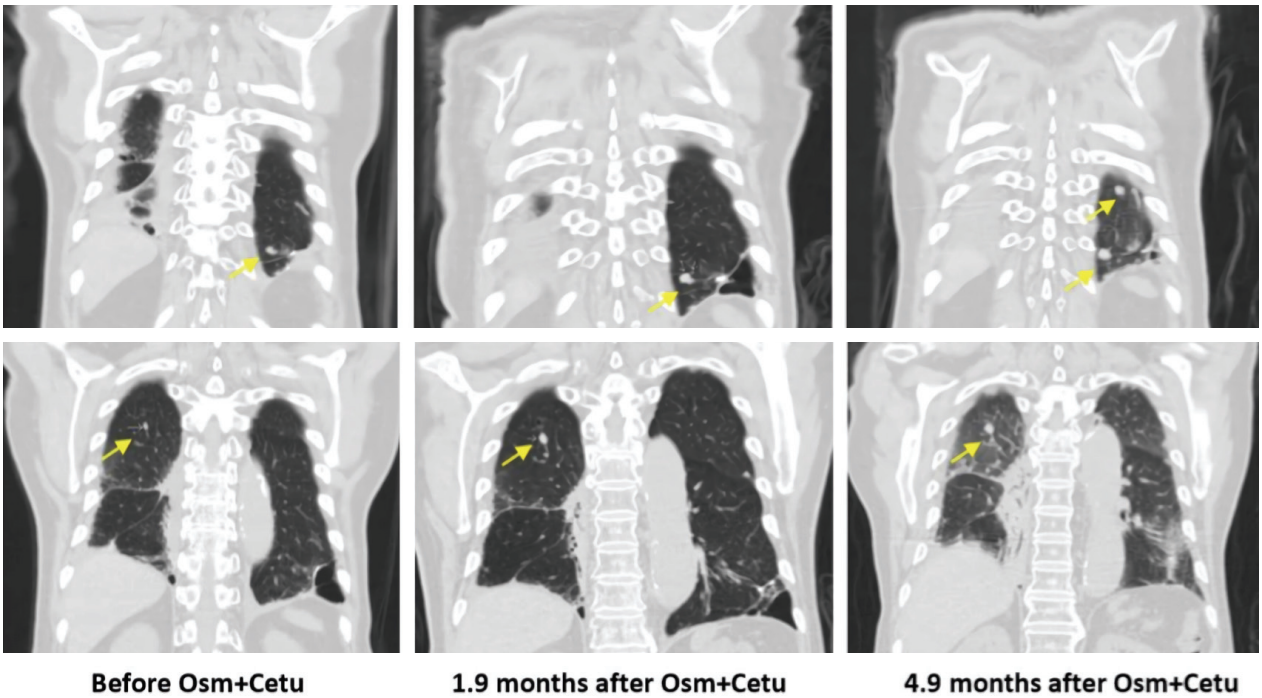


Fig. 2. Case 2: The patient had EGFR T790M and C797S mutation-positive NSCLC. Osimertinib 80 mg daily and cetuximab 250 mg/m^2 biweekly were prescribed. PFS was 4.9 months. (Osm: Osimertinib; Cetu: Cetuximab)

noted. Osimertinib 80 mg daily and cetuximab 250 mg/m^2 biweekly were then prescribed as the next regimen. He then experienced SD for 4.9 months. At that point, follow-up imaging showed that the lung metastasis had increased in size (Table 1 and Figure 2).

Case 3: A 64-year-old woman was diagnosed with NSCLC. She initially tested positive for an exon 19 deletion. She received TKIs, including erlotinib, afatinib and osmertinib sequentially, based on the EGFR mutation. After 7.7 months of osimertinib use, EGFR T790M combined with a C797S mutation were found. She was then treated with osimertinib 80 mg daily and cetuximab 200 mg/m^2 every 2 weeks. She had SD for 4.1 months with this combination, until new lung and brain metastases were detected (Table 1, Figure 3).

Case 4: This 61-year-old woman's initial diagnosis was exon 21 L858R mutation-positive NSCLC. She took gefitinib, erlotinib, and then osimertinib sequentially, based on the EGFR mutation. After 4.8 months of osimertinib treatment, EGFR T790M and C797S-positive NSCLC were found. Osimertinib 80 mg daily and cetuximab 250 mg/m^2 every 2 weeks were used as the next treatment. Bilateral lung metastasis progressed 1 month later and she then passed away (Table 1 and Figure 4).

Discussion

In our retrospective chart review of 4 patients, 3 with both EGFR T790M and C797S mutation-positive NSCLC seemed to have benefited from osimertinib and cetuximab use. The PFS of these 3 patients was 6.7, 4.9, and 4.1 months, respectively.

Cetuximab, an EGFR monoclonal antibody, was approved for treatment of KRAS wild-type

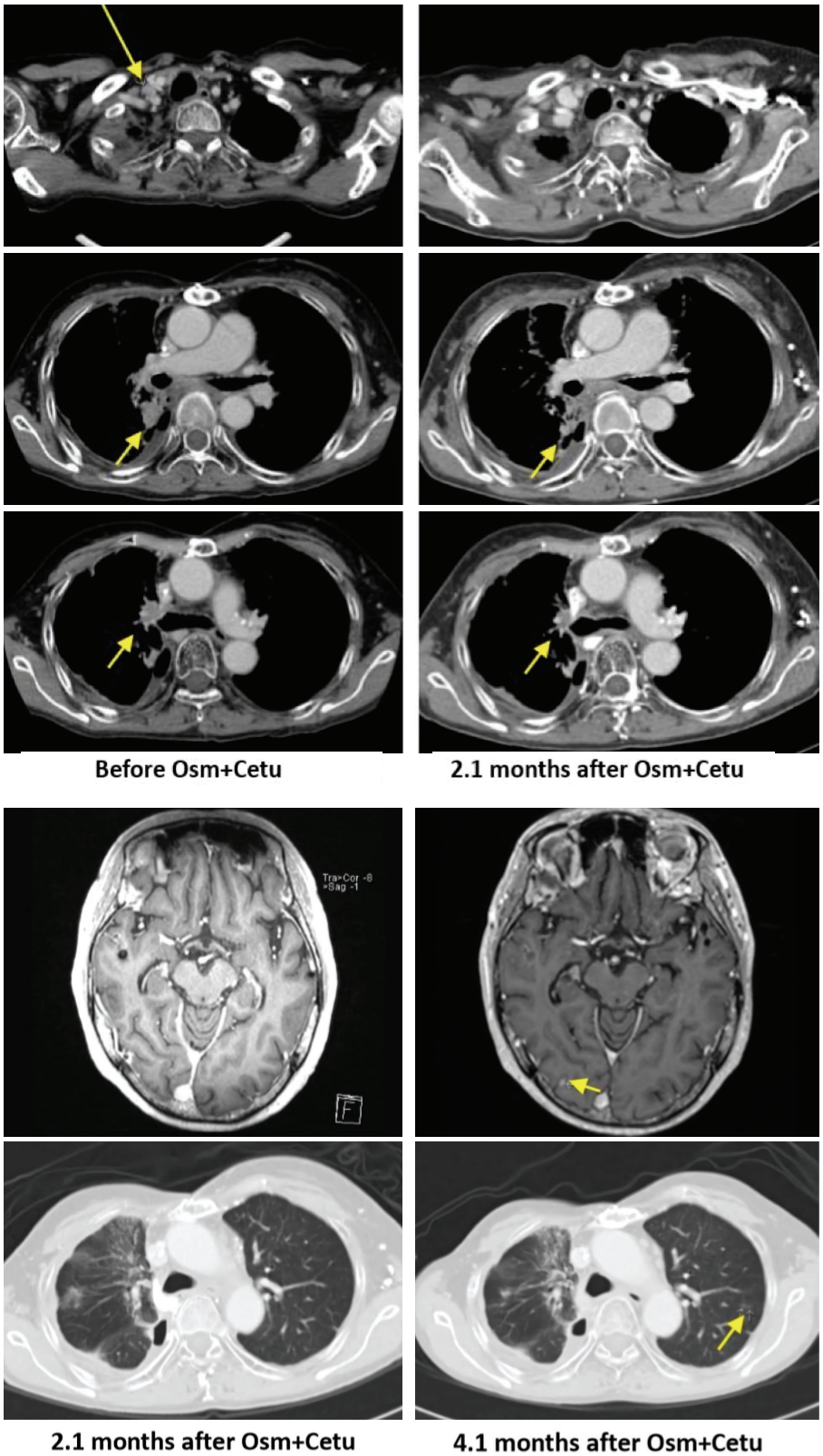


Fig. 3. Case 3: The patient was diagnosed with EGFR T790M and C797S mutation-positive NSCLC. Osimertinib 80 mg daily and cetuximab 200 mg/m^2 biweekly were used. PFS was 4.1 months. (Osm: Osmertinib; Cetu: Cetuximab)

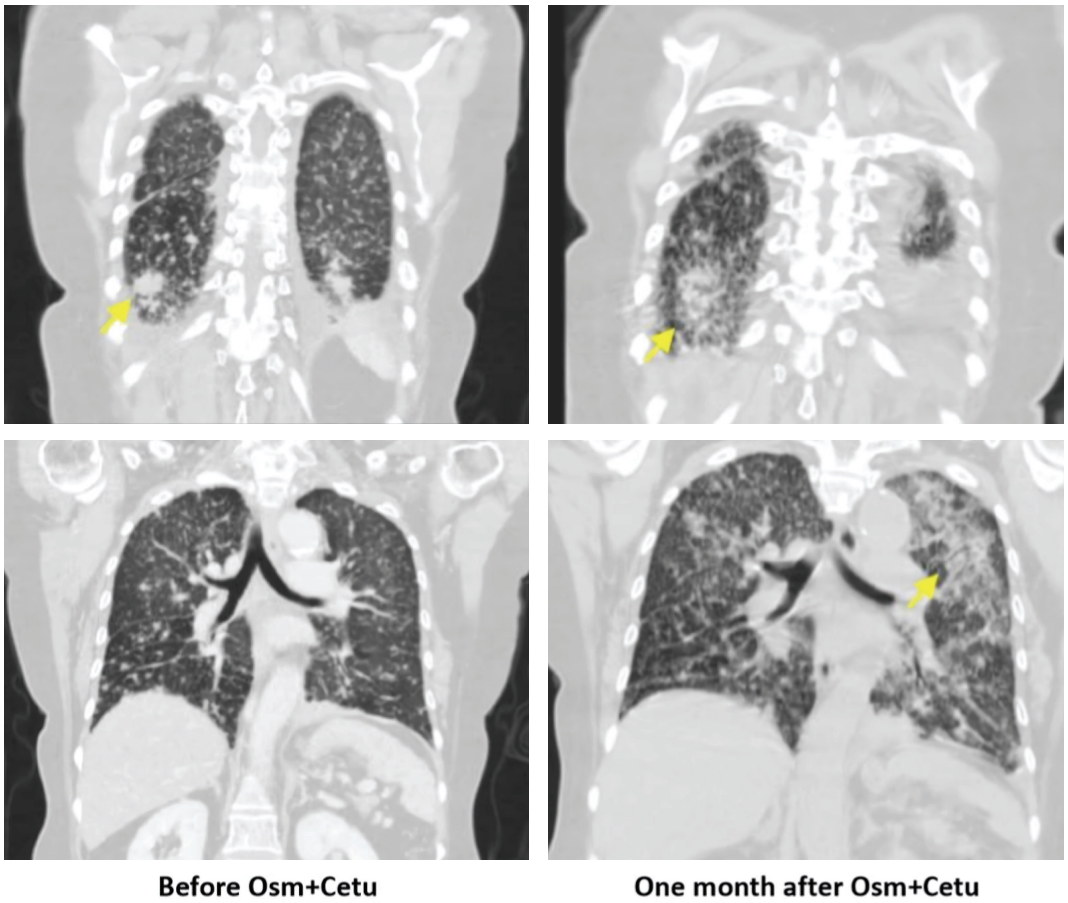


Fig. 4. The patient's diagnosis was EGFR T790M and C797S mutation-positive NSCLC. Osimertinib 80 mg daily and cetuximab 250 mg/m^2 biweekly were used. PFS was 1 month. (Osm: Osmertinib; Cetu: Cetuximab)

colorectal cancer and head and neck cancer [12]. In an animal study, afatinib, combined with cetuximab had better efficacy than either agent alone for mice with both L858R and T790M mutation-positive lung cancer [13]. Several human trials have demonstrated that afatinib plus cetuximab had modest response in patients with erlotinib or gefitinib resistant EGFR mutation-positive NSCLC [14-16]. Multiple mechanisms for this combination have been proposed. One possibility is that afatinib and cetuximab target different receptors and may have a synergic effect. A second possibility is that afatinib promotes binding of cetuximab to the cell surface so the efficacy of cetuximab increases [15]. The NCCN guideline suggests that afatinib and cetuximab may be used with EGFR mutation-positive NSCLC patients with disease progression while under treatment with EGFR TKIs such as erlotinib, gefitinib or afatinib [3].

A previous study reported that cetuximab, combined with brigatinib, a dual EGFR-ALK inhibitor, overcame EGFR T790M and C797S mutations in NSCLC patients treated with osimertinib [17]. We wanted to know whether cetuximab could restore the efficacy of osimertinib in treating for osimertinib-resistant EGFR mutations in NSCLC patients, achieving a synergic effect similar to that of afatinib for erlotinib or gefitinib-resistant EGFR mutation

NSCLC. A previous animal study indicated that when combined with cetuximab, osimertinib was as effective as second-line therapy for osimertinib-resistant NSCLC mice. The treatment response rate was 50~66.6%, and no significant toxicities were found [10]. However, similar research in humans is absent. Our case series found that the combination of osimertinib and cetuximab seemed to prolong the efficacy of osimertinib for EGFR T790M mutation-positive NSCLC.

Conclusions

Osimertinib, combined with cetuximab seemed to be beneficial for NSCLC patients with acquired T790M and C797S positive NSCLC. Further studies are necessary in order to understand the mechanism.

References

1. Key statistics for lung cancer, America Cancer Society https://www.cancer.org/cancer/non-small-cell-lung-cancer/about/key-statistics.html
2. Proto C, Lo Russo G, Corrao G, *et al*. Treatment in EGFR-mutated non-small cell lung cancer: how to block the receptor and overcome resistance mechanisms. Tumori 2017; 103(4): 325-37.
3. Zhang YL, Yuan JQ, Wang KF, *et al*. The prevalence of EGFR mutation in patients with non-small cell lung cancer: a systematic review and meta-analysis. Oncotarget 2016; 7(48): 78985-93.
4. Xu J, Yang H, Jin B, *et al*. Corrigendum: EGFR tyrosine kinase inhibitors versus chemotherapy as first-line therapy for non-small cell lung cancer patients with the L858R point mutation. Sci Rep 2016; 6: 38270.
5. NCCN guideline, version I, 2019 Non-small Cell Lung Cancer https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf
6. Tan CS, Kumarakulasinghe NB, Huang YQ, *et al*. Third generation EGFR TKIs: current data and future directions. Mol Cancer 2018; 17(1):29.
7. Pinion S. Osimertinib improves progression-free survival in NSCLC. Lancet Respir Med 2017; 5(4): 251.
8. Wang S, Tsui ST, Liu C, *et al*. EGFR C797S mutation mediates resistance to third-generation inhibitors in T790M-positive non-small cell lung cancer. J Hematol Oncol 2016; 9(1): 59.
9. Chen L, Fu W, Zheng L, *et al*. Recent progress of small-molecule epidermal growth factor receptor (EGFR) inhibitors against C797S resistance in non-small-cell lung cancer. J Med Chem 2018; 61(10): 4290-300.
10. Della Corte CM, Ciaramella V, Cardone C, *et al*. Antitumor efficacy of dual blockade of EGFR signaling by osimertinib in combination with selumetinib or cetuximab in activated EGFR human NCLC tumor models. J Thorac Oncol 2018; 13(6): 810-20.
11. Eisenhauer EA, Therasse P, Bogaerts J, *et al*. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45(2): 228-47.
12. Harding J, Burtness B. Cetuximab: an epidermal growth factor receptor chemeric human-murine monoclonal antibody. Drugs Today (Barc) 2005; 41(2): 107-27.
13. Regales L, Gong Y, Shen R, *et al*. Dual targeting of EGFR can overcome a major drug resistance mutation in mouse models of EGFR mutant lung cancer. J Clin Invest 2009; 119(10): 3000-10.
14. van Veggel B, de Langen AJ, Hashemi SMS, *et al*. Afatinib and cetuximab in four patients with EGFR exon 20 insertion-positive advanced NSCLC. J Thorac Oncol 2018; 13(8): 1222-6.
15. Janjigian YY, Smit EF, Groen HJ, *et al*. Dual inhibition of EGFR with afatinib and cetuximab in kinase inhibitor-resistant EGFR-mutant lung cancer with and without T790M mutations. Cancer Discov 2014; 4(9): 1036-45.
16. Horn L, Gettinger S, Camidge DR, *et alI* . Continued use of afatinib with the addition of cetuximab after progression on afatinib in patients with EGFR mutation-positive non-small-cell lung cancer and acquired resistance to gefitinib or erlotinib. Lung Cancer 2017; 113: 51-8.
17. Uchibori K, Inase N, Araki M, *et al*. Brigatinib combined with anti-EGFR antibody overcomes osimertinib resistance in EGFR-mutated non-small-cell lung cancer. Nat Commun 2017; 8:14768.

Intralobar Bronchopulmonary Sequestration with Congenital Cystic Adenomatoid Malformation in an Adult

Kuan-Liang Chen[1,3], Yi-Jia Lin[2], Tsai-Wang Huang[1]

Pulmonary sequestration (PS) and congenital cystic adenomatous malformation (CCAM) are both rare congenial disorders with similar etiologies. PS derives a vascular supply from systemic circulation, but does not connect to the tracheobronchial tree. CCAM is characterized by the formation of a cyst with a pulmonary vascular supply that connects to the tracheobronchial tree. Intrapulmonary PS rarely occurs with CCAM. We describe the case of a 63-year-old woman who had intrapulmonary PS, with pathology results indicating a coexistence with CCAM. ***(Thorac Med 2020; 35: 91-95)***

Key words: intralobar bronchopulmonary sequestration, congenital cystic adenomatoid, malformation, adult

Introduction

Congenital cystic adenomatoid malformation (CCAM) and bronchopulmonary sequestration (BPS) are both congenital cystic malformations of the lung and both may lead to respiratory distress [1]. There are 2 subtypes of BPS: intralobar sequestration (ILS) and extralobar sequestration (ELS). The presence of any co-occurring congenital anomalies is rarer in ILS than in ELS [2]. Here, we present the case of an adult female who had a hybrid ILS and CCAM lesion.

Case Report

The patient was a 63-year-old female; she was a non-smoker and had no systemic diseases. She had had 3 previous episodes of pneumonia (in the right lower lobe) and had undergone care for this in hospitals outside of our country during the 5 years preceding her presenting to our outpatient department with pneumonia complaints. On examination, her heart rate was 68 beats per minute; her respiratory rate was 16 breaths per minute. The physical examination was non-remarkable except for a crackle in the

[1]Division of Thoracic Surgery, Tri-Service General Hospital, National Defense Medical Center; [2]Department of Pathology, Tri-Service General Hospital, National Defense Medical Center; [3]Division of Thoracic Surgery, Zuoying Branch of Kaohsiung Armed Forces General Hospital
Address reprint requests to: Dr. Tsai-Wang Huang, Division of Thoracic Surgery, Tri-Service General Hospital, National Defense Medical Center, No. 325, Sec 2, Cheng-Kung Road, Taipei 114, Taiwan (R.O.C.)

bilateral lower lung field.

We did not find leukocytosis or an increased neutrophil/lymphocyte ratio. The immunoglobulin E level was 1166.0 IU/μL. The erythrocyte sedimentation rates were 1166.0 IU/μL. The anti-RO and anti-LA levels were both normal, and the blood cryptococcus antigen assay was negative. The chest plain film showed ill-defined patchy infiltrations in the right lower lung (RLL) zone and an increased density in the right infrahilar region. With suspected pneumonia, the patient was admitted for further examinations.

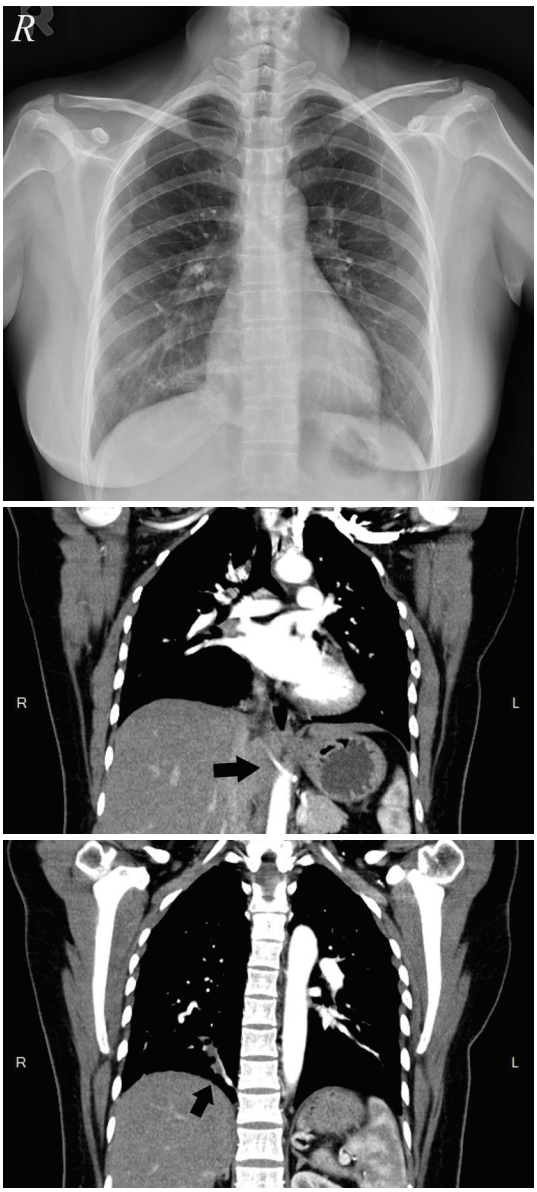


Fig. 1. Upper: Chest plain film showed ill-defined patchy opacities in the right lower lung zone. Middle and lower: Computed tomography revealed small areas of irregular soft-tissue opacities with a feeding artery from the descending aorta and venous return to the pulmonary vein (black arrow)

The posteroanterior chest view and computed tomography (CT) revealed small areas of irregular soft-tissue opacities, with a feeding artery derived from the descending aorta and venous return to the pulmonary vein via multiple small cystic lesions in the RLL, suggestive of intrapulmonary sequestration (Figure 1). We used a Fujifilm Synapse 3D system to reconstruct the arterial and venous trees, based on chest CT (Figure 2).

The patient's preoperative forced expiratory volume in 1 second (FEV1) was 2.81 liters. This was 85.3% of the predicted normal; her preoperative carbon monoxide lung diffusion capacity (DLCO) was 17.92 ml/mmHg/min, which was 74.9% of the predicted normal.

Operative findings indicated blood-congestion of the right lower lobe of the lung within the feeding artery and vein; there was no extrapulmonary pleural sac. The feeding artery

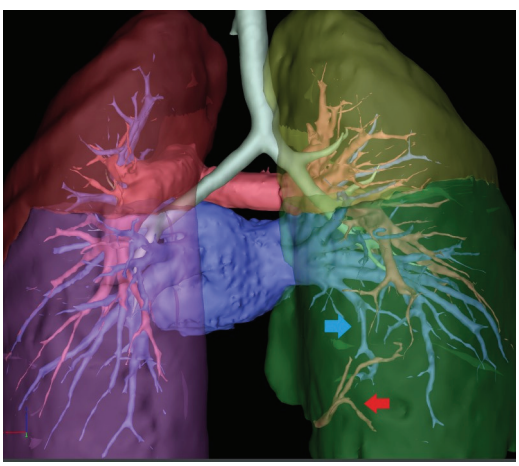


Fig. 2. Feeding artery (red arrow) and vein (blue arrow) based on chest computed tomography.

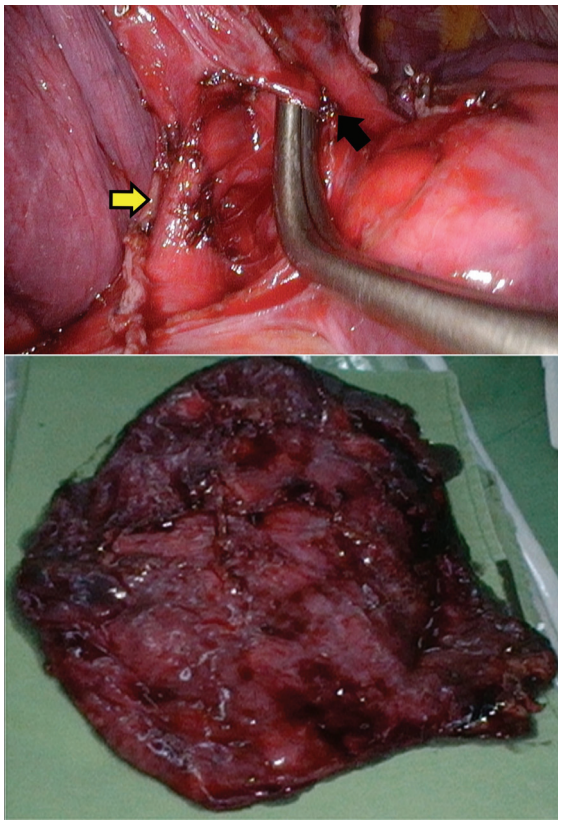


Fig. 3. Uniportal video-assisted thoracoscopic surgery with lobectomy of the sequestrated lung at the right lower lung revealing (upper) a feeding artery (black arrow) and vein (yellow arrow) and (lower) blood congestion of the right lower lobe of the lung.

did not originate from the pulmonary system. The feeding artery and drainage vein were ligated; uniportal video-assisted thoracoscopic surgery with lobectomy of the sequestrated lung at the RLL was performed (Figure 3).

Microscopy examination indicated dilated, irregularly shaped bronchi in the distal airways with ciliated epithelium (hematoxylin and eosin [H&E], original magnification x400) (Figure 4) and an anomalous artery supply (H&E, original magnification x40) (Figure 5). The microcystic air space was lined with cuboidal epithelium (H&E, original magnification x100) (Figure 6). This was compatible with pulmonary sequestration with Type II CCAM. Ac-

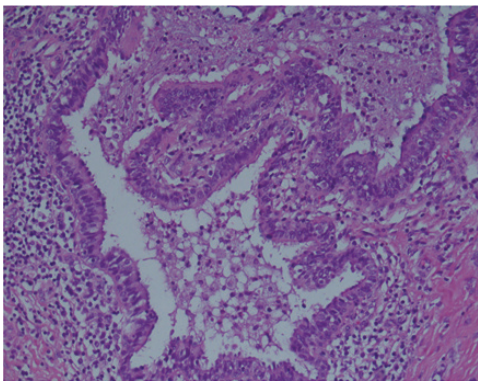


Fig. 4. Dilated irregularly-shaped bronchi in distal airways with ciliated epithelium (H&E, original magnification x400).

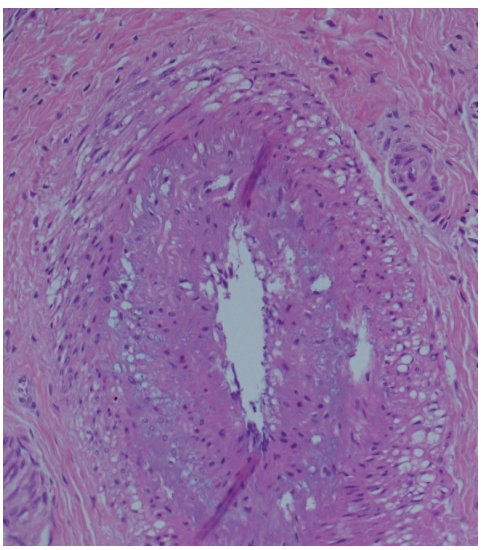


Fig. 5. Anomalous artery supply (H&E, original magnification x40) compatible with pulmonary sequestration.

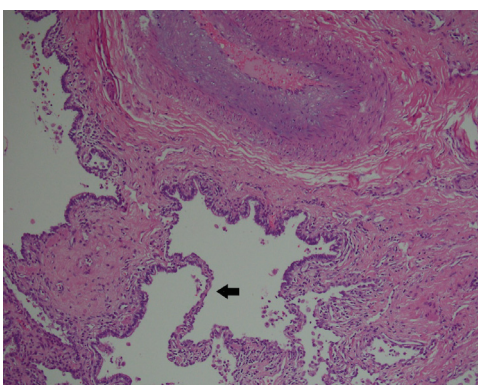


Fig. 6. Microcystic air space lined with cuboidal epithelium (H&E, original magnification x100) compatible with Type II CCAM.

id-fast stain and bacterial culture were negative. The patient was discharged in stable condition on the fifth postoperative day and was followed up at our outpatient department.

Discussion

Pulmonary maldevelopment results in lung bud anomalies, such as congenital lobar emphysema, congenital lung cysts, CCAM, sequestrations, and bronchogenic cysts. Both CCAM and sequestrations are rare, and contribute to <15% of pediatric cystic lung lesions. CCAM is a malfunction in the development of lung buds, and is characterized by multiple cystic changes and bronchiole proliferation. The incidence of CCAM has ranged from 1:25,000 to 1:35,000. Type I CCAM is characterized as 1 or more dominant cysts, 2–10 cm in size; Type I comprises 55% of reported cases. Type II CCAM is characterized as presenting with numerous cysts, <2 cm in diameter; this form of CCAM comprises 40% of cases. Type III CCAM is characterized by adenomatoid proliferation in the distal airways or air spaces, with cysts that are usually <5 mm in diameter; this manifestation of CCAM comprised 5% of cases. Though the etiology of CCAM is not wholly clear, it is widely believed that CCAM is caused by poor bronchoalveolar development within the pulmonary mesenchyme.

The male:female ratio is 1:1, with respiratory distress being a typical symptom [3]. Common CCAM symptoms during infancy are chronic cough and/or recurrent pneumonia. A prenatal ultrasound scan aids early detection. CCAM in adults is rare and is usually related to chronic pulmonary infection [4].

Sequestrations are non-communicating pulmonary lesions with a systemic vascular supply. The incidence of sequestrations ranges from 0.15%–1.8% in the general population. ILS is 3 times more common than ELS. ILS is contained within a normal lung bud. ELS has its own pleural lining, and is anatomically separated from the adjacent lung. ILS typically occurs in the posterior basal region (60%), with a male:female ratio of 1:1. The systemic blood supply of ILS originates from the descending aorta; venous drainage is via the pulmonary vein [5]. A simultaneous occurrence of ILS and CCAM is exceptionally rare in adulthood, with only 2 cases so far described in the English-language medical literature (Table 1) [6,11]. We resected the lesions in our case with video-assisted thoracic lobectomy, although previous cases were treated with open lobectomy. However, we were treating an older patient, and in this case, recurrent respiratory symptoms were the main reason for surgical resection.

The most common pathological result in our literature review was hybrid Type II CCAM and ILS. Mastrogiulio et al. indicated that the morphology of hybrid ILS and type 2 CCAM is associated with chronologically abnormal development between the mesoderm and endoderm that ultimately leads to defects [7].

Cystic changes are common in ILS, and in adults, an infection is usually the cause. In ILS, morphologically cystic lesions are unicystic or polycystic, and are usually caused by bronchiectasis and cystic adenomatoid malformation [8]. Samuel *et al*. reported 5 infants who had PS with co-occurring Type II CCAM; 2 cases were associated with ILS [9].

To prevent recurrent respiratory infections, management for both symptomatic ILS and CCAM is surgical resection; however, endovascular embolization is an alternative, less invasive approach to ILS management, and can

Table 1. List of Simultaneous Occurrence of ILS and CCAM Described so far

Patient	Presentation	Age	Location	Surgery	Aberrant vessel	Histology	Follow-up
1	Chronic cough	20	RLL	Right lower lobectomy via thoracotomy	Yes	CCAM + ILS	well
2	Pneumonia	36	LLL	Left inferior lobectomy	Yes	CCAM type 2+ ILS	well
3 (Our case)	Pneumonia	63	RLL	Video-assisted thoracoscopic lobectomy	Yes	CCAM type 2+ ILS	well

be performed when appropriate [5]. However, when performing surgical resection for CCAM without identifying ILS, there is an increased risk of bleeding [10].

In conclusion, our case demonstrated an extremely rare occurrence of both ILS and Type II CCAM. We suggest it is important to distinguish between ILS and CCAM with a differential diagnosis in adults who have a history of recurrent pulmonary infections.

References

1. Ballian N, Weigel TL. Sabiston and Spencer's Surgery of the Chest, 8th ed. (Review) J Surg Res 2011; 167:206.
2. Ravenel JG. Imaging of Diseases of the Chest, 5th ed. (Review) J Thorac Imaging 2010; 25:W100.
3. earson's Thoracic & Esophageal Surgery. 3rd ed. Pearson FG, Patterson GA, editors. Philadelphia: Churchill Livingstone/Elsevier; 2008.
4. Patz EF, Müller NL, Swensen SJ, *et al*. Congenital cystic adenomatoid malformation in adults: CT findings. J Comput Assist Tomogr 1995; 19: 361-4.
5. Almeida Sequeira TC, Antunes N, Bento L, *et al*. Pulmonary sequestration: Beyond surgery…. Eur Respir J 2016; 48: PA3824.
6. Silva E, Vale J, Reis A. Late onset congenital cystic adenomatous malformation associated with intralobar pulmonary sequestration. Revista Portuguesa de Pneumologia 2015; 21: 282-4.
7. Mastrogiulio MG, Barone A, Disanto MG, *et al*. Type II congenital pulmonary airway malformation associated with intralobar pulmonary sequestration: Report of a case and review of classification criteria. Pathologica 2016; 108: 38-41.
8. Savic B, Birtel FJ, Tholen W, *et al*. Lung sequestration: report of seven cases and review of 540 published cases. Thorax 1979; 34: 96-101.
9. Samuel M, Burge DM. Management of antenatally diagnosed pulmonary sequestration associated with congenital cystic adenomatoid malformation. Thorax 1999; 54(8): 701-6.
10. Sfakianaki AK, Copel JA. Congenital cystic lesions of the lung: congenital cystic adenomatoid malformation and bronchopulmonary sequestration. Rev Obstet Gynecol 2012; 5: 85-93.
11. Chung TJ, Cheng LL, Chang HY, *et al*. Adult-onset congenital cystic adenomatoid malformation in combination with intralobar bronchopulmonary sequestration: A case report. Chin J Radiol 2004; 29(4): 213-216.