

Original Article

Comparison of impulse oscillometry and traditional pulmonary function tests in chemotherapy of lung cancer

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Abstract: Objective: To compare the clinical application value of impulse oscillometry (IOS) and traditional pulmonary function tests (PFTs) in chemotherapy of lung cancer. Methods: Eighty-nine patients with pathologically confirmed stage IIIB-IV non-small-cell lung cancer that were hospitalized in the Department of Respiratory Medicine of The First Affiliated Hospital of Quanzhou, Fujian Medical University from October 2010 to May 2012 were selected for the study and assessed by IOS and traditional PFTs. Among the 89 patients, 67 with clinical benefits, 26 with central type, 26 with peripheral type, and 15 associated with pleural effusion showed partial response (PR) or stable disease (SD) after 2 cycles of chemotherapy (Gemcitabine combined with Cisplatin or Nedaplatin). Additionally, 22 ineffective patients (9 with central type; 11 with peripheral type; 2 associated with pleural effusion) were evaluated as progressive disease (PD). Results: When detecting lung function via traditional PFTs instrument, the patients with peripheral or central lung cancers had significantly higher forced vital capacity than those associated with pleural effusion ($P=0.0403$, $P=0.0410$, respectively). The patients with central lung cancer or associated with pleural effusion had a lower ratio of forced expiratory volume in 1 second to predicted value (FEV_1/pre) than those with peripheral lung cancer ($P=0.0316$, $P=0.0192$, respectively). After 2 cycles of chemotherapy, patients with PR or SD had improved total airway resistance (R_5), ratio of R_5 to predicted value (R_5/pre), central airway resistance (R_{20}) and ratio of R_{20} to predicted value (R_{20}/pre) as compared with those before chemotherapy when detecting the lung function via IOS instrument (all $P<0.0001$). However, there were no significant difference in lung function before and after chemotherapy among patients with PD when detecting the lung function via traditional PFTs instrument or IOS instrument (all $P>0.05$). Conclusion: R_5 and R_{20} measured by IOS can be used as one of the indices judging the marked effect of chemotherapy in patients with lung cancer. The application of IOS appears to be more indicative of the chemotherapeutic efficacy and prognosis than traditional PFTs in patients with lung cancer.

Keywords: Impulse oscillometry, lung function, lung cancer, chemotherapy

Introduction

The incidence of lung cancer continues to increase globally. It is the most common malignant tumor in men, accounting for 17% of new cancer cases and 23% of cancer related deaths, whereas in developing countries, the incidence of lung cancer has increased rapidly among women [1]. In 2014, an estimated 3,804,000 new cases of cancer were diagnosed in China (incidence rate 278.07/100,000), and 2,296,000 people died from the disease (mortality rate 167.89/100,000) [2]. Currently, the efficacy of lung cancer treatment is still unsatisfactory and most patients with lung cancers are detected only in the advanced stages and therefore miss the opportunity of surgical

resection. Therefore, chemotherapy is still one of the most common methods for the treatment of advanced lung cancer [3].

Impulse oscillometry (IOS) is a variation of the forced oscillation technique for testing pulmonary function by calculating respiratory impedance. It can detect the changes in viscous resistance, elastic resistance and inertial resistance, leading to an increased understanding of pulmonary function [4]. There are obvious differences between IOS and traditional pulmonary function tests (PFTs) in regard to the rationale and indicators. IOS has higher sensitivity in detecting obstructive airway diseases and will not be affected by bronchial dilation caused by labored breathing, which contribute to the

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Table 1. Comparison of general data between the two groups of patients

	Group A	Group B	Group C	P
Case	35	37	17	
Gender				0.2550
Male	19	27	11	
Female	16	10	6	
Age (years)	63.69±9.03	61.50±7.93	64.40±9.09	0.4110

Note: Group A, peripheral lung cancer; group B, central lung cancer; group C, lung cancer associated with pleural effusion.

early diagnosis and evaluation of diseases [5]. Moreover, IOS can better reflect the airway obstruction, chest (lung) lesions and the existence, nature and severity of other related lesions. A good lung function as indicated by these tests corresponds to better quality of life in patients with lung cancer [6].

Currently, IOS is widely used in the diagnosis of chronic obstructive pulmonary disease, while there are few reports on the comparison of the use of IOS and traditional PFTs in China for detecting the lung function changes and its significance in patients with lung cancers. We used the MasterScreen IOS and traditional PFTs to detect lung function in patients with lung cancers who had received chemotherapy, so as to compare their clinical application value.

Materials and methods

Patient information

Samples were selected from a total of 89 patients with pathologically confirmed stage IIIB-IV non-small-cell lung cancer (NSCLC) that were hospitalized in the Department of Respiratory Medicine of The First Affiliated Hospital of Quanzhou, Fujian Medical University from October 2010 to May 2012. Among the 89 patients, 67 had clinical benefits, 26 with central type, 26 with peripheral type, and 15 associated with pleural effusion showed partial response (PR) or stable disease (SD) after 2 cycles of chemotherapy (Gemcitabine combined with Cisplatin or Nedaplatin). Additionally, 22 ineffective patients (9 with central type; 11 with peripheral type; 2 associated with pleural effusion) was evaluated as progressive disease (PD). These patients were not diagnosed with concomitant chronic obstructive pulmonary

disease according to the chronic obstructive pulmonary disease diagnostic criteria of Global Initiative for Obstructive Lung Disease and Respiratory Diseases Branch of Chinese Medical Association [1, 2].

This study was approved by the Ethics Committee of The First Affiliated Hospital of Quanzhou, Fujian Medical University and informed consent was obtained from all patients.

Methods

Lung function tests were performed in all 89 patients with lung cancers before and after 2 cycles of chemotherapy, by a trained clinician familiar with the routine operating requirements of traditional PFTs (SensorMedics, USA) and IOS instrument (Jaeger, Germany). All subjects completed IOS tests before the ventilation function and lung volume tests, so as to avoid the effects of forced exhalation on the airway tension and the IOS measurements that were taken according to the recommended criteria of European Respiratory Society [3].

Lung function parameters included forced vital capacity (FVC), ratio of forced vital capacity to predicted value (FVC/pre), ratio of the residual volume to total lung capacity (RV/TLC), forced expiratory volume in 1 second (FEV1), ratio of forced expiratory volume in 1 second to predicted value (FEV1/pre), peak expiratory flow (PEF), and the ratio of peak expiratory flow to predicted value (PEF/pre). IOS parameters included the resonant frequency (Fres), ratio of Fres to predicted value (Fres/pre), total airway resistance (R5), ratio of R5 to predicted value (R5/pre), central airway resistance (R20), ratio of R20 to predicted value (R20/pre), and the respiratory reactance at oscillating frequency of 5 Hz (X5) [7, 8].

Evaluation criteria

The efficacy of the tests was evaluated by Response Evaluation Criteria in Solid Tumors criteria, and outcomes were divided into complete response (CR), PR, SD, and PD [4]. In this study, there were no patients with CR due to only 2 cycles of chemotherapy, and we defined PR and SD as clinical benefits and PD as clinical ineffectiveness.

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Table 2. Comparison of indicators of lung function detected via traditional PFTs instrument before chemotherapy

	Group C vs. group A		Group C vs. group B		Group B vs. group A	
	Mean difference	P	Mean difference	P	Mean difference	P
Age (years)	0.7077	0.8114	2.9000	0.8114	-2.1923	0.3884
FVC	-0.5090	0.0403	-0.5111	0.0410	0.0021	0.9921
FVC/pre	-0.1983	0.0041	-0.1104	0.1067	-0.0879	0.1338
RV/TLC	0.0284	0.4469	-0.0122	0.7467	0.0407	0.2446
FEV1	-0.2716	0.1315	-0.1265	0.4832	-0.1450	0.3493
FEV1/pre	-0.1309	0.0316	-0.0073	0.9036	-0.1235	0.0192
PEF	-0.0054	0.9905	0.2727	0.5504	-0.2781	0.4778
PEF/pre	-0.0147	0.8113	0.0813	0.1930	-0.0961	0.0742

Note: Group A, peripheral lung cancer; group B, central lung cancer; group C, lung cancer associated with pleural effusion. FVC, forced vital capacity; FVC/pre, the ratio of forced vital capacity to predicted value; RV/TLC, the ratio of the residual volume to total lung capacity; FEV1, forced expiratory volume in 1 second; FEV1/pre, the ratio of forced expiratory volume in 1 second to predicted value; PEF, peak expiratory flow; PEF/pre, the ratio of peak expiratory flow to predicted value; PFTs, pulmonary function tests.

Table 3. Comparison of indicators of lung function detected via IOS instrument before chemotherapy

	Group C vs. group A		Group C vs. group B		Group B vs. group A	
	Mean difference	P	Mean difference	P	Mean difference	P
Age (years)	0.7077	0.8114	2.9000	0.8114	-2.1923	0.3884
R5	-0.1861	0.7630	-0.5203	0.4000	0.3342	0.5270
R5/pre	-0.0060	0.9759	-0.1726	0.3869	0.1665	0.3293
R20	-0.1842	0.5765	-0.2915	0.3774	0.1073	0.7036
R20/pre	-0.0327	0.8314	-0.0989	0.5016	0.0663	0.5998
X5	-0.1237	0.9684	0.1778	0.9571	-0.3015	0.8294
Fres	0.6890	0.7849	-1.0783	0.6693	1.7673	0.4138
Fres/pre	0.1292	0.6346	-0.1901	0.4845	0.3192	0.1715

Note: Group A, peripheral lung cancer; group B, central lung cancer; group C, lung cancer associated with pleural effusion. R5, total airway resistance; R5/pre, the ratio of R5 to predicted value; R20, the central airway resistance; R20/pre, the ratio of R20 to predicted value; X5, the respiratory reactance at oscillating frequency of 5 Hz; Fres, resonant frequency; Fres/pre, the ratio of Fres to predicted value. IOS, impulse oscillometry.

Statistics analysis

SPSS20.0 software was used for statistical analysis. The one-way analysis of variance with a Games-Howell post hoc test was used for dealing with heterogeneity of variance. The one-way analysis of variance with a Fisher's Least Significant Difference test method was used for dealing with homogeneity of variance. The t test was used for comparison before and after chemotherapy. $P < 0.05$ indicates that the difference is statistically significant.

Results

General data

Patients with peripheral type of NSCLC (group A, without concomitant pleural effusion) included 19 males and 16 females aged 45 to 78

years, with a mean age of 63.69 ± 9.03 years old. The patients with central type (group B, without concomitant pleural effusion) included 27 males and 10 females aged 40 to 75 years, with a mean age of 61.50 ± 7.93 years old. The patients of lung cancer associated with pleural effusion (group C) included 11 males and 6 females aged 40 to 78 years old, with a mean age of 64.40 ± 9.09 years old. There were no significant differences between the groups in terms of general data (both $P > 0.05$) as shown in **Table 1**.

Comparison of indicators of lung function detected via traditional PFTs instrument or IOS instrument before chemotherapy

As shown in **Tables 2** and **3**, before chemotherapy, FVC of group A and group B was significant-

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Table 4. Comparison of lung function detected via traditional PFTs instrument before and after 2 cycles of chemotherapy in 67 patients with clinical benefits

	Before chemotherapy	After chemotherapy	P
FVC	2.5275±0.8134	2.6950±0.7439	0.2158
FVC/pre	0.7875±0.2246	0.8625±0.2148	0.0503
RV/TLC	0.3350±0.0332	0.3290±0.0419	0.3599
FEV1	1.9700±0.6473	2.0825±0.4858	0.2573
FEV1/pre	0.7750±0.1949	0.8300±0.1268	0.0550
PEF	5.3925±1.9134	5.7625±1.1298	0.1752
PEF/pre	0.8600±0.1695	0.9075±0.2191	0.1628

Note: FVC, forced vital capacity; FVC/pre, the ratio of forced vital capacity to predicted value; RV/TLC, the ratio of the residual volume to total lung capacity; FEV1, forced expiratory volume in 1 second; FEV1/pre, the ratio of forced expiratory volume in 1 second to predicted value; PEF, peak expiratory flow; PEF/pre, the ratio of peak expiratory flow to predicted value; PFTs, pulmonary function tests.

Table 5. Comparison of lung function detected via IOS instrument before and after 2 cycles of chemotherapy in 67 patients with clinical benefits

	Before chemotherapy	After chemotherapy	P
R5	3.7900±0.8451	3.1600±0.6249	<0.0001
R5/pre	1.1050±0.2466	0.9200±0.1857	<0.0001
R20	3.2025±0.5261	2.8175±0.5604	<0.0001
R20/pre	1.0875±0.1884	0.9550±0.1448	<0.0001
X5	-1.4860±0.7536	-1.4220±0.7059	0.4960
Fres	18.3492±4.7165	16.7900±5.4313	0.0783
Fres/pre	1.8810±0.6583	1.8936±0.4423	0.8967

Note: R5, total airway resistance; R5/pre, the ratio of R5 to predicted value; R20, the central airway resistance; R20/pre, the ratio of R20 to predicted value; X5, the respiratory reactance at oscillating frequency of 5 Hz; Fres, resonant frequency; Fres/pre, the ratio of Fres to predicted value. IOS, impulse oscillometry.

ly higher than that of group C (both $P < 0.05$) and the FEV1/pre of group B and group C was significantly lower than that of group A (both $P < 0.05$) when detecting the lung function via traditional PFTs instrument. Furthermore, none of the detected indicators showed a difference between the three groups with IOS instrument.

Comparison of lung function detected via traditional PFTs instrument or IOS instrument before and after 2 cycles of chemotherapy in 67 patients with clinical benefits

As shown in **Tables 4** and **5**, when detecting the lung function via traditional PFTs instrument, none of the indicators showed a difference after chemotherapy. However, R5, R5/pre, R20,

and R20/pre were improved after chemotherapy (all $P < 0.0001$) when detecting the lung function via IOS instrument.

Comparison of lung function detected via traditional PFTs instrument or IOS instrument before and after 2 cycles of chemotherapy in 22 ineffective patients

As shown in **Tables 6** and **7**, when detecting the lung function via traditional PFTs instrument or IOS instrument, the differences in all the detected indicators of lung function tests were insignificant before and after 2 cycles chemotherapy (all $P > 0.05$).

Discussion

FEV1 refers to the volume of air that can be exhaled during a forced breath in one second, and is the most commonly used indicator to determine the degree of ventilation function damage and reversibility of airway obstruction to guide surgical treatment [9]. This study found that the FEV1/pre ratios of patients with central lung cancer and pleural effusion were significantly lower than that of patients with peripheral lung cancer, which suggests that the former group of patients had more serious damage of lung ventilation function and clinical symptoms (such as dyspnea and cough). Some studies have suggested that the ratios of

FEV1/FVC and X5 are the leading indicators of the accuracy in predicting postoperative respiratory failure [10]. We found that there was less reduction in lung function in patients with peripheral lung cancer, so it was considered early peripheral lung cancer might have a lighter degree of lung function reduction, high tolerance of surgery, and small possibility of postoperative respiratory failure. The FVC of patients with peripheral and central lung cancers were significantly higher than patients associated with pleural effusion, which was considered to be related to the limited thoracic motions caused by pleural effusion. Studies have shown impedance measured over low frequencies or total frequencies, increased resistance and its difference at the ends of inspiration and expira-

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Table 6. Comparison of lung function detected via traditional PFTs instrument before and after 2 cycles of chemotherapy in 22 ineffective patients

	Before chemotherapy	After chemotherapy	P
FVC	2.4195±0.8116	2.4250±0.7185	0.9811
FVC/pre	0.7795±0.2306	0.7715±0.2188	0.9066
RV/TLC	0.3280±0.0318	0.3190±0.0572	0.5224
FEV1	1.8900±0.6395	1.8725±0.4698	0.9181
FEV1/pre	0.7540±0.1706	0.7458±0.1032	0.8480
PEF	5.1795±1.7286	5.0875±1.0974	0.8341
PEF/pre	0.7805±0.1598	0.7798±0.2164	0.9903

Note: FVC, forced vital capacity; FVC/pre, the ratio of forced vital capacity to predicted value; RV/TLC, the ratio of the residual volume to total lung capacity; FEV1, forced expiratory volume in 1 second; FEV1/pre, the ratio of forced expiratory volume in 1 second to predicted value; PEF, peak expiratory flow; PEF/pre, the ratio of peak expiratory flow to predicted value; PFTs, pulmonary function tests.

Table 7. Comparison of lung function detected via IOS instrument before and after 2 cycles of chemotherapy in 22 ineffective patients

	Before chemotherapy	After chemotherapy	P
R5	3.9840±0.8451	3.9978±0.6318	0.9514
R5/pre	1.3160±0.2596	1.3386±0.1908	0.7438
R20	3.4108±0.5374	3.4385±0.5725	0.8694
R20/pre	1.1265±0.1906	1.1287±0.1496	0.9662
X5	-1.7590±0.7689	-1.8060±0.7458	0.8379
Fres	17.5987±4.9667	17.1980±5.3256	0.7976
Fres/pre	1.8560±0.6625	1.8469±0.4524	0.9578

Note: R5, total airway resistance; R5/pre, the ratio of R5 to predicted value; R20, the central airway resistance; R20/pre, the ratio of R20 to predicted value; X5, the respiratory reactance at oscillating frequency of 5 Hz; Fres, resonant frequency; Fres/pre, the ratio of Fres to predicted value; IOS, impulse oscillometry.

tion, and reversed positions in intra-breath diagrams of patients with pleural effusion [11, 12]. However, we found no significant differences between patients with concomitant pleural effusion and those with central and peripheral lung cancers. Studies have also suggested that the determination of respiratory resistance was insignificant in the identification of lung cancer types, but there was a certain significance in judging lung function damage in patients with lung cancer [13-15].

In this study, the average Fres of patients with lung cancers were all more than 15 Hz, suggesting a certain degree of obstructive or restrictive ventilatory dysfunction. Fres is also a diagnostic parameter for airway hyper-responsive-

ness with the highest sensitivity and specificity among all IOS parameters [16]. In this study however, neither the 67 patients with clinical benefits nor the 22 ineffective patients experienced any significant changes in lung function after 2 cycles of chemotherapy, suggesting a general lack of sensitivity in detecting chemotherapeutic efficacy in patients with lung cancers. X5 indicates peripheral elastic resistance (not just the lungs). The X5 examination data in our study indicated an increase in reactance from all groups, suggesting that each type of lung cancer (especially the central type) could cause reduced lung dynamic compliance and peripheral air-flow obstruction.

Lung cancers can cause partial or complete bronchial blocking, atelectasis, or obstructive inflammation, local compression of organs and tissues, pleural effusion as well as changes in respiratory resistance because of the infiltration, metastasis, and diffusion of cancer cells. All of these changes would lead to corresponding changes in Fres, R5, R20, and X5 [17-19]. Airway resistance R from low frequency to high frequency reflects the airway resistance change from peripheral to central tissues. R5 (total respiratory resistance) and R20 (central airway resistance) values changed in patients with all types of lung cancers, suggesting changes in the airway resistance. Furthermore, the difference between R5 and R20 was significant,

suggesting that patients with each type of lung cancer had different degrees of airway obstruction. By assessing 67 patients with stage IIIB-IV NSCLC who had clinical benefits from 2 cycles of chemotherapy (Gemcitabine combined with Cisplatin or Nedaplatin) (SD and PR) and 22 patients who had no clinical benefits from chemotherapy (PD) by IOS and traditional PFTs, we found that R5, R5/pre, R20, and R20/pre improved after chemotherapy (all $P < 0.05$). Other indicators however were not significantly different. There was no significant difference in lung function before and after chemotherapy in 22 patients with PD ($P > 0.05$), suggesting that R5 and R20 in IOS method could be used as the indicators to determine the chemothera-

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peutic efficacy in patients with lung cancers. It is possible that changes in lung function after chemotherapy were an indirect result of effective chemotherapy, whereby the tumors shrunk in size and led to transient improvement in lung function, reduction and disappearance of pleural effusion, improvement in airway obstruction and compression, and a decrease in airway resistance.

In addition, we believe that chemotherapy not only did no harm to the lung function of patients with clinical benefits, but also had no significant effects on pulmonary function of patients with PD. It had been found that systemic chemotherapy by intravenous drip and anti-cancer treatment by pulmonary artery perfusion for bronchogenic carcinoma had no effects on respiratory function, which was consistent with our findings [20].

This study has certain limitations, such as the limited sample size and no evaluation of the combination of IOS and traditional PFTs. We will further improve the study protocol, enlarge the sample size, and do a more in-depth study.

In summary, R5 and R20 in the IOS method can be used as indicators to determine the efficacy of chemotherapy in patients with lung cancers, and compared with traditional PFTs, IOS can better indicate efficacy of chemotherapy and prognosis in patients with lung cancers.

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Disclosure of conflict of interest

None.

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