Ventilation in patients with stage IIIB or above lung cancer

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Background: To investigate the distribution of lung function and ventilation dysfunction in patients with locally advanced and advanced lung cancer, and the correlation with clinical factors.

Methods: A retrospective study was conducted on patients who were discharged from the respiratory department of our hospital and diagnosed with locally advanced (IIIB, IIIC) or advanced (IVA, IVB) lung cancer from October 2013 to October 2020. Demographic information, clinical data, and lung function assessments were recorded, and the proportion and type of ventilation dysfunction and the correlations between them and clinical factors were statistically analyzed.

Results: A total of 130 patients were included. Han nationality accounted for 99.2%, and males accounted for 79.2% of patients. The average age was 68.48±10.77 years old. In terms of the stage of lung cancer, the proportion of locally advanced IIIB/IIIC was 34.6%, and the proportion of advanced IVA/IVB was 65.4%. The lung function results were as follows: forced expiratory volume in the first second (FEV1)/forced vital capacity (FVC) was 72.27% (62.35%, 79.60%), FEV1/vital capacity (VC) was 71.35% (61.78%, 79.20%), FEV1 was 1.72±0.64 L, VC was 2.44±0.70 L, and total lung volume (TLC) was 4.41±0.97 L. Obstructive, restrictive, and mixed ventilation dysfunction accounted for 23.1%, 26.9%, 27.7%, respectively, and 93.1% had not received lung function screening or treatment before. A total of 42 cases (32.3%) had moderate or above obstruction or mixed (mainly obstruction) ventilation dysfunction. The most common symptoms were cough (88.1%), expectoration (71.4%), and dyspnea (40.5%). The chi-square test showed that male, ≥70 years old, smoking history, smoking index ≥800 years, accompanied by airway diseases [chronic obstructive pulmonary disease (COPD)/asthma/chronic bronchitis], and computed tomography (CT) with atelectasis accounted for a higher proportion (P<0.05). Logistic regression showed that age (P=0.003), smoking history (P=0.04), atelectasis (P=0.004), and associated airway diseases (P=0.001) were significant related factors.

Conclusions: Some patients with locally advanced or advanced lung cancer have ventilation dysfunction, especially moderate or above obstruction or mixed (mainly obstruction) ventilation dysfunction. For vulnerable populations such as males, the elderly, long-term heavy smokers, patients with airway diseases, or patients with atelectasis on CT, lung function assessment and intervention should be improved to further manage the symptom control and quality of life of patients with this type of lung cancer.

Keywords: Locally advanced and advanced lung cancer; lung function; ventilation dysfunction

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Introduction

Lung function assessment is an important method to evaluate respiratory function integrity and to identify the damage type and degree of severity, and is the diagnostic gold standard for bronchial asthma and chronic obstructive pulmonary disease (COPD). It is also often used in the fields of lung cancer, preoperative risk assessment, or functional evaluation of patients with shortness of breath and other symptoms and differential screening of patients with combined airway diseases. In order to explore the characteristics of lung function and ventilation dysfunction in patients with locally advanced and advanced lung cancer, this study retrospectively collected the clinical information of patients with stage IIIB, IIIC, IVA, or IVB diagnosed in our hospital from October 2013 to October 2020, and the analytical results are as follows. We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/atm-21-2203).

Methods

Study participants

We had conducted a cross-sectional study. The data of study participants in this retrospective study were collected between October 2013 to October 2020 in our respiratory hospital. Patients were diagnosed with locally advanced (IIIB, IIIC) or late (IVA, IVB) stage lung cancer. Records included social demographic information such as gender and age, as well as clinical information (such as lung pathological type, stage, chest imaging, symptoms, medical history, lung function).

Lung function examination

The patient was placed in the upright position and the whole body was relaxed. The patient gently bit the mouth, the lips were closed as the mouth could not have gaps, and a nose clamp was used to clamp nostrils. The most important movements in the examination were to inhale and exhale through the mouth, keeping the nostrils dry. Vital capacity (VC), forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), rate in one second (FEV1/FVC), ratio of forced expiratory volume in the first second to vital capacity (FEV1/VC), total lung volume (TLC), and other indexes of the patients were measured. The volume error was ≤±3%, and the best value out of 3 times was taken as the recorded result.

Diagnostic criteria

Locally advanced and advanced lung cancer

Diagnosis was based on the 2018 edition of the Chinese Medical Association Clinical Guidelines for the Diagnosis and Treatment of Lung Cancer (1), and staging was based on the 8th edition of TNM staging published in the 2016 issue of *JTO* (*Journal of Thoracic Oncology*) (2). Stage IIIB and IIIC were locally advanced, while stage IVA and IVB were advanced.

Lung function

The standard was based on the 2018 edition of the guidelines for lung function examination of the Chinese Respiratory Association. According to the ratio of forced expiratory volume in the first second to vital capacity (FEV1/VC), vital capacity (VC), total lung capacity (TLC) is greater than or equal to the normal limit (LLN) was divided into normal, obstructive ventilation dysfunction, restrictive ventilatory dysfunction, and mixed ventilation dysfunction. FEV1/VC LLN was estimated at 92% of the value, and the rest of the lung function index LLN was 80% of the expected value. In patients with ventilation dysfunction, the severity was graded according to the percentage of FEV1 in the predicted value (FEV1%): mild (FEV1% ≥70%, but < LLN or FEV1/FVC < LLN), moderate (FEV1% in 60–69%), moderate to severe (FEV1% in 50–59%), severe (FEV1% in 35–49%), very severe (FEV1% <35%).

Statistical analysis

Statistical analyses were performed using SPSS 19.0 software (IBM Corporation, America). Descriptive statistics were used to analyze all data. Measurement data with a normal distribution were expressed as mean ± standard deviation, and the independent sample t test was used for comparisons between groups. Measurement data with a non-normal distribution were expressed as medians (quartile), and comparisons between different groups were performed using the Mann-Whitney U test. Patients were grouped into subgroups according to different social demographics and clinical characteristics. Enumeration data were expressed as percentages, with chi-squared tests used for inter-group comparisons. Univariate and multivariate logistic regression analyses were conducted for factors with statistical significance. P<0.05 was considered statistically significant.

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Ruijin Hospital (Shanghai, China) “(2021) Clinical Ethics Approval No. 112”. Because the medical records and other information were obtained from previous clinical practice, and investigation did not adversely

Table 1 Baseline data of patients with locally advanced and advanced lung cancer

Variable	Total number, n=130 (%)	Moderate or above obstruction or mixed ventilation dysfunction, n=42 (%)	Non-moderate or above obstruction or mixed ventilation dysfunction, n=88 (%)	P value
Male	103 (79.2)	40 (38.8)	63 (61.2)	0.002*
Han nationality	129 (99.2)	42 (32.6)	87 (67.4)	1.000
Age ≥70 years old	61 (46.9)	29 (47.5)	32 (52.5)	0.000*
BMI <24 kg/m^2	71 (54.6)	28 (39.4)	43 (60.6)	0.057
Occupational retirement	102 (78.5)	37 (36.3)	65 (63.7)	0.065
With smoking history	98 (75.4)	39 (39.8)	59 (60.2)	0.001*
Smoking index ≥800 years	58 (44.6)	24 (41.4)	34 (58.6)	0.047*
With dust exposure history	3 (2.3)	1 (33.3)	2 (66.7)	1.000
With airway disease	49 (37.7)	28 (7.1)	21 (42.9)	0.000*
With other pulmonary diseases	10 (7.7)	4 (40.0)	6 (60.0)	0.726
Pathological type of lung cancer				0.469
Non-small cell carcinoma	104 (80.0)	36 (34.6)	68 (65.4)	
Small cell carcinoma	23 (17.7)	5 (21.7)	18 (78.3)	
Others	3 (2.3)	1 (33.3)	2 (66.7)	
Clinical staging of lung cancer				0.832
IIIB, IIIC	45 (34.6)	14 (31.1)	31 (68.9)	
IVA, IVB	85 (65.4)	28 (32.9)	57 (67.1)	
Chest CT findings				
Multiple lesions	44 (33.8)	15 (34.1)	29 (65.9)	0.756
With tracheobronchial obstruction	48 (36.9)	17 (35.4)	31 (64.6)	0.562
With atelectasis	28 (21.5)	14 (50.0)	14 (50.0)	0.024*
With pulmonary exudation or consolidation	29 (22.3)	7 (24.1)	22 (75.9)	0.286
With interstitial pneumonia	6 (4.6)	2 (33.3)	4 (66.7)	1.000
With pleural effusion	60 (46.2)	24 (40.0)	36 (60.0)	0.083

*, P value represents the difference between groups of moderate or higher obstruction or mixed ventilation dysfunction after the chi-square test, and <0.05 indicates a statistically significant difference. CT, computed tomography.

affect the rights and health of the subjects, the requirement for informed consent was waived.

Results

Baseline data

A total of 130 patients diagnosed with locally advanced or advanced lung cancer who underwent lung function assessment were investigated. Baseline data are shown in *Table 1*.

General population information

Han nationality accounted for 99.2%. Males accounted for 79.2% of the population, and patients were aged between

35–96 years old, with an average age of 68.48±10.77 years old. Body mass index (BMI) of patients ranged from 15.43–33.09 kg/m^2, with an average of 23.52±3.42 kg/m^2. Retired patients accounted for 78.5%, 2.3% had dust exposure history, and 75.4% had a smoking history with a smoking index of 800 [600–1,200] years. Furthermore, 37.7% of the patients had airway diseases (COPD/asthma/chronic bronchitis), while 7.7% had other pulmonary diseases (tuberculosis/interstitial pulmonary disease/sleep apnea-hypopnea syndrome/thoracic pulmonary surgery), and 93.1% had not received previous screening and treatment of lung function. Finger oxygen saturation was 91–99%, 97% (95%, 99%).

Lung cancer diagnosis

The clinical stage of lung cancer was locally advanced IIIB/IIIC in 45 cases (34.6%) and advanced IVA/IVB in 85 cases (65.4%). Among the pathological types, 104 cases (80%) were non-small cell carcinoma (adenocarcinoma, squamous cell carcinoma, adenosquamous cell carcinoma, large cell/giant cell carcinoma), 23 cases (17.7%) were small cell carcinoma, and 3 cases (2.3%) were other (neuroendocrine/poorly differentiated carcinoma). CT findings showed that 66.2% of the lesions were single, 36.9% showed tracheobronchial obstruction, 21.5% showed atelectasis, 22.3% showed consolidation and exudation of pneumonia, 4.6% showed interstitial pneumonia, and 46.2% showed pleural effusion.

Results of lung function

FEV1/FVC were 27.41–99.70%, 72.27% (62.35%, 79.60%). FEV1/VC were 35.10–99.70%, 71.35% (61.78%, 79.20%), and FEV1 ranged from 0.57 to 3.64 L, with an average of 1.72±0.64 L. VC ranged from 0.89 to 4.15 L, with an average of 2.44±0.70 L. TLC ranged from 2.17 to 7.81 L, with an average of 4.41±0.97 L. There were 30 patients (23.1%) with obstructive ventilation dysfunction, 35 patients (26.9%) with restrictive ventilation dysfunction, 36 patients (27.7%) with mixed ventilation dysfunction, and 29 patients (22.3%) with normal pulmonary function. A total of 42 cases (32.3%) had moderate or above obstruction or mixed (mainly obstruction) ventilation dysfunction. Among them, the most common symptoms were cough (88.1%), expectoration (71.4%), and dyspnea (40.5%), which were higher than those of patients with non-moderate or above obstruction or mixed ventilation dysfunction (31.8%, P=0.332).

Analysis of the related factors of moderate or above obstruction or mixed ventilation dysfunction

The chi-square test showed that the incidence of moderate or above obstruction or mixed ventilation dysfunction in men was higher than that in women (P=0.0002), and was higher in patients ≥70 years old than that in patients <70 years old (P=0.000). Patients with a smoking history also had a higher incidence of moderate or above obstruction or mixed ventilation dysfunction (P=0.001) compared to those with no smoking history, and patients with a smoking index ≥800 also had a higher incidence than those with a smoking index <800 (P=0.047). Patients with airway diseases had a higher incidence of moderate or above obstruction or mixed ventilation dysfunction than those without airway diseases (P=0.000), and patients with atelectasis on CT also had a higher incidence than those without atelectasis (P=0.024). There were no significant differences in other factors such as nationality, occupation, BMI, pathological type, stage, and location of lung cancer (*Table 1*).

Univariate and multivariate Logistic regression analysis was conducted for the statistically significant factors obtained from the above tests to further analyze the correlation. Age (P=0.003), smoking history (P=0.04), atelectasis (P=0.004), and airway disease (P=0.001) were the significant factors associated with moderate or higher obstruction or mixed ventilation dysfunction in locally advanced/advanced lung cancer patients (P<0.05, *Table 2*).

Discussion

Lung cancer is a heterogeneous disease whose occurrence and development are jointly affected by environmental exposure and genetic susceptibility. Environmental factors include smoking, air pollution, indoor air pollution, and occupational carcinogen exposure, amongst others (1,3). Studies have shown that lung cancer is still the most common type of cancer in China, with a statistical estimate of 787,000 new cases in 2015, and nearly 30% of cancer-related deaths are attributed to lung cancer, which brings a heavy burden on patients' families, social health, and the economy (4).

Lung function assessment can evaluate the quality and quantity of the basic respiratory physiology function of subjects, and can detect the variability of lung function impairment. It is of great significance to explore the

Table 2 Univariate and multivariate regression analysis of moderate or higher obstruction or mixed ventilation dysfunction

Variable	Univariate			Multivariate		
	OR	95% CI	P value	OR	95% CI	P value
Male	0.126	0.028–0.561	0.007			NS
Age ≥70 years old	3.904	1.780–8.561	0.001	4.029	1.595–10.174	0.003
With smoking history	6.390	1.820–22.428	0.004	4.208	1.066–16.608	0.040
Smoking index ≥800 years	2.118	1.004–4.468	0.049			NS
With airway disease	6.381	2.846–14.306	0.000	5.117	2.014–13.000	0.001
With atelectasis on CT	2.643	1.119–6.239	0.027	5.276	1.685–16.520	0.004

OR, risk ratio; CI, confidence interval; CT, computed tomography; NS, there was no significant difference.

pathogenesis, pathology, and physiology of diseases in order to aid in diagnosis, guide treatment, judge the curative effect and disease rehabilitation, and to evaluate chest surgery tolerance, amongst other factors (5). In the clinical practice of lung cancer, lung function assessment is often used for bronchoscopy, function and risk assessment before thoracic surgery, or for screening patients with dyspnea and other symptoms for complications (COPD or bronchial asthma).

There have been previous reports on the association between surgery for early lung cancer and lung function assessment and follow-up (6-8), however, few patients with advanced lung cancer were targeted. Therefore, this study explored lung function in locally advanced and advanced lung cancer patients, and analyzed the distribution and related factors of ventilation dysfunction.

Studies have reported that most patients with lung cancer have abnormal lung function, with a higher incidence rate than healthy people, including early small airway obstruction, obstructive ventilation dysfunction, restrictive ventilation dysfunction, and mixed ventilation dysfunction (5,9). Carbon monoxide dispersion (DLCO) in lung cancer patients with COPD was significantly lower than that in patients with COPD alone (10). This is related to the following pathophysiological mechanisms: the obstruction of the trachea/bronchus caused by the compression of cancer tissue causes obstructive pneumonia and atelectasis; the reduction in lung volume, limited ventilation function, and reduced diffuse area caused by pleural lesions; the compensation of surrounding lung tissue increases ventilation, resulting in an imbalance of ventilation/blood flow ratio; cancer compression of blood vessels, blocked blood flow, reduced blood flow, increased ventilation/blood flow ratio; cancer cells can metastasize through the blood stream and block small blood vessels, leading to further imbalance of ventilation/blood flow ratio, decreases in VC and ventilation, and an increase in residual air volume (5). In this study, the overall rate of abnormal lung function in patients with locally advanced and advanced lung cancer was 77.7%, which was similar to the literature. Dyspnea was more common in patients with moderate or higher obstruction or mixed ventilation dysfunction (mainly obstruction), accounting for 32.3%.

In elderly people, due to physiological decline, the elastic retraction force of lung tissue and the thoracic compliance decrease, leading to varying degrees of reductions in lung function with the increase in age, which is more obvious if combined with lung diseases and lung function damage (11). Luoto *et al.* followed up the elderly population aged 60–102 years and found that the annual average variation rates of FEV1 and FVC were −51.7 (−63.3–−39.9) mL and −56.2 (−73.6–−38.8) mL, respectively. The annual average variation rates of FEV1 and FVC were −2.97% (−3.53–−2.40%) and −2.46% (−3.07–−1.85%), respectively (12). In patients with locally advanced and advanced lung cancer in this study, age ≥70 years old was significantly correlated with moderate or above obstruction/mixed ventilation dysfunction, and the age characteristics were consistent with the literature reports. Moreover, due to malignant tumors and advanced or terminal stages of disease, the consumption of nutrients and physical strength can often affect respiratory muscle strength and ventilation function. We found a higher incidence of moderate or higher obstructive/mixed ventilation dysfunction in patients with lower BMI (<24 kg/m^2), but this was not statistically significant (P=0.057).

COPD, bronchial asthma, and bronchiectasis are common chronic airway diseases. Long-term airway inflammation and bronchial and alveolar structural remodeling/destruction can lead to ventilation/blood flow ratio imbalance, increased residual air, decreased dispersion, and obstructive ventilation dysfunction as the main manifestation (13). In comparison, Zhao *et al.* found that 63.6% of COPD patients with lung cancer were advanced or partially advanced when first diagnosed, and the DLCO was significantly lower than that of the control group (P<0.05) (10). In this study, airway diseases such as COPD were significantly associated with moderate or above obstruction/mixed ventilation dysfunction in locally advanced and advanced lung cancer patients, and DLCO was significantly lower than that in patients without airway diseases, which was similar to the results in the literature.

Smokers are known to be a high-risk group for lung cancer, and tobacco smoke is also a major risk factor for chronic airway inflammation, emphysema, and COPD (13,14). Smoking first causes damage to small airways, and further causes damage to lung tissue structures, which can lead to bronchospasms and increases airway resistance, mucus impaction, and repeated infection. It can also damage pulmonary blood vessels, causing hardening of the wall, thinning of the lumen, reduction of pulmonary blood flow, and decrease of lung gas exchange function (14). In addition to cigarettes, pipe and cigar smoking is also associated with decreased lung function and an increased risk of airflow disruption, and may have an effect on people who have never smoked cigarettes before (15). Smoking cessation is an effective improvement method, which can effectively reduce the annual decline of FEV1, especially in men (16). In this study, smoking was found to be a significant correlation factor for locally advanced and advanced lung cancer patients with moderate or above obstructive/mixed ventilation dysfunction. For patients with a history of smoking, attention should be paid to the assessment of lung function, as well as early detection and intervention in the routine diagnosis and treatment of lung cancer.

Lung cancer may be caused by local atelectasis changes due to obstruction of a neoplasm in the airway, compression of extraperitoneal mass/enlarged lymph node, or compression of pleural effusion. Obstructive atelectasis has been reported in about 1/5 cases of small cell lung cancer (17). Radiotherapy and chemotherapy can also be complicated by atelectasis (18). In this study, atelectasis was significantly associated with moderate or higher obstructive/mixed ventilation dysfunction in patients with locally advanced and advanced lung cancer. Such patients often have lymph node, pleura, and other metastases, are susceptible to complicated atelectasis, one or more lung segments or lobes or reduced volume or gas content, alveolar gas absorption, or other lung tissue compensatory emphysema, which then produces obstruction or mixed ventilation dysfunction. It is necessary to formulate a reasonable lung cancer treatment strategy for this group of people, including appropriate chemotherapy, radiotherapy with adjusted site dose (19), and close follow-up imaging and lung function assessment during treatment.

In this study, moderate or higher obstruction/mixed ventilation dysfunction was not significantly associated with the pathological types and clinical stages of locally advanced and advanced lung cancer, suggesting that significant ventilation dysfunction is an independent complication of this type of lung cancer. Dyspnea is a common symptom of locally advanced to advanced lung cancer patients, and is associated with abnormal lung function and is also a clinical marker of survival and prognosis of the disease (20). In non-small cell lung cancer (NSCLC), FEV1 can predict the risk of radiation pneumonia after concurrent chemoradiotherapy (21) and is a survival prognostic factor for stage IIIB or IV patients (22,23). Improved lung function is associated with increased activity tolerance, and 6-minute walking distance (6MW) ≥400 m is the only significant beneficial factor for predicting survival in patients with advanced NSCLC (24). Therefore, it is of great significance to explore the diagnosis and treatment of pulmonary function and ventilation dysfunction in patients with locally advanced to advanced lung cancer.

There are still some shortcomings in this study. First, only lung function and the probability of ventilation dysfunction and related factors in locally advanced and advanced lung cancer patients were studied, and other clinical stage patients were not included for control analysis. Secondly, this was only a single-center retrospective study, limiting the number of patients examined. In the future, we will consider expanding the scope of the study and set up a comparative population to prospectively explore more meaningful indicators of lung function in lung cancer.

Conclusions

The present study found that some patients with locally advanced and advanced lung cancer had combined ventilation dysfunction, especially moderate or above obstruction or mixed (mainly obstruction) ventilation dysfunction, which was significantly associated with older age, smoking history, airway disease, and atelectasis. This suggests that in the process of the clinical diagnosis and treatment of lung cancer, we should not only perform routine lung function assessments before invasive surgery, but we also need to emphasize the lung function assessment of locally advanced and advanced patients in addition to their anti-tumor treatment. If there is a patient with obvious ventilation dysfunction, in addition to monitoring the signs and symptoms such as dyspnea and finger oxygen saturation, doctors can consider using a long-acting bronchodilator or even double-branched diffuser, referring to the treatment recommendations for COPD, in order to improve the clinical symptoms, lung function index, and quality of life.

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Footnote

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