A study of the application of fiberoptic bronchoscopy combined with liquid-based cytology test in the early diagnosis of lung cancer

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Abstract. Application value of fiberoptic bronchoscopy combined with liquid-based cytology test (LCT) in the early diagnosis of lung cancer was investigated. Clinical data of 901 patients who had suspicious lung space-occupying lesions and underwent bronchoscopy combined with LCT in Shanxi Provincial Cancer Hospital from June 2012 to June 2016 were retrospectively analyzed. Patients were divided into four groups to receive different fiberoptic bronchoscopies combined with LCT. Patients in Group A (n=276) received bronchoscopic washing cultures (BWC), Group B (n=204) received bronchoalveolar lavage (BAL), Group C (n=187) underwent endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and Group D (n=234) underwent transbronchial lung biopsy (TBLB). All patients received pathological biopsy to confirm the lesions. The diagnostic results of lung cancer and the incidence rates of postoperative adverse reactions/complications were analyzed and compared among the four groups. Among 901 patients, 741 cases were pathologically diagnosed with lung cancer. In Group A, there were 224 cases diagnosed with lung cancer, of which 193 cases were successfully detected with a detection rate of 86.17% and a κ-value of 0.426. In Group B, 171 cases were diagnosed with lung cancer, of which 149 cases were successfully detected with a detection rate of 87.13% and a κ-value of 0.430. In Group C, 154 cases were diagnosed with lung cancer, of which 146 cases were successfully detected with a detection rate of 94.81% and a κ-value of 0.769. In Group D, 192 cases were diagnosed with lung cancer, of which 170 cases were successfully detected with a detection rate of 88.54% and a κ-value of 0.440. Therefore, we conclude that fiberoptic bronchoscopy combined with LCT technique is safe and reliable for the diagnosis of the early-stage lung cancer.

Introduction

According to reports of the World Health Organization (WHO) and other international authoritative agencies, incidence and mortality rates of lung cancer in China are increasing year by year, and China has the largest number of lung cancer patients worldwide (1-3). In spite of the efforts that have been made for the treatment of this disease, the average survival time after drug treatment is only 3-5 months (4). However, 5-year survival rates can be as high as 60-70% after early diagnosis and early operation (4). Therefore, it is of great clinical value to develop a more effective technique to improve the early diagnosis of lung cancer. Lesion tissues can be observed through a fiberoptic bronchoscope for pathological examination to definitely diagnose lung cancer. However, a fiberoptic bronchoscope is not effective for the identification of early-stage tumors due to the location or size, while cytology may compensate this deficiency. The development of cytology test techniques and the clinical application of liquid-based cytology test (LCT) technique (5-7) have significantly improved the diagnosis of chest and lung cancer, malignant pleural effusion and other non-gynecological diseases (8-11). According to the different methods used for cytology sample collection, fiberoptic bronchoscopy techniques can be divided into bronchoscopic washing cultures (BWC), bronchoalveolar lavage (BAL), endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and transbronchial lung biopsy (TBLB) techniques (12-18). The combination of fiberoptic bronchoscopy and LCT can not only improve the diagnosis of the disease but also reduce the incidence of complications (16-18). In this study, LCT was combined with four different cytology sample-obtaining methods for the early diagnosis of lung malignant tumors, and satisfactory outcomes were reached.

Patients and methods

Study subjects. In the present retrospective study, clinical data were selected from 901 patients who received fiberoptic bronchoscopy in Shanxi Provincial Cancer Hospital (Taiyuan,

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China) from June 2012 to June 2016. The inclusion criteria were: i) patients primarily diagnosed with lung space-occupying lesions by clinical or imageological examination; ii) patients who received bronchoscopy combined with LCT; and iii) patients diagnosed by fiberoptic bronchoscopy for suspicious lesions, surgical lung biopsy or percutaneous puncture pathological examination. The 901 patients included 579 males [age range from 25 to 84 years with an average age of 57.1±10.65 years] and 322 females [age ranged from 27 to 81 years with an average age of 55.2±11.35 years]. All patients underwent bronchoscopy under awakened state to obtain cytology samples. All patients signed the informed consent.

Diagnostic methods. Patients with suspicious lung malignant lesions diagnosed by imageological examination were selected. According to the methods used to obtain cytology samples through bronchoscope, patients were divided into Groups A-D. Group A was treated with bronchoscopic washing cultures (BWC), Group B was treated with bronchoalveolar lavage (BAL), Group C was treated with endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and Group D was treated with transbronchial lung biopsy (TBLB); in combination with LCT technique, respectively. At the same time, all patients received fiberoptic bronchoscopy, surgery and percutaneous puncture pathological biopsy for definite diagnosis. Patients' responses were closely observed during diagnosis and operation and their vital signs were monitored. The diagnostic results of all groups were compared and analyzed. Related indicators of four fiberoptic bronchoscopies combined with LCT in the diagnosis of lung cancer and the incidence rates of adverse reactions/complications were recorded and analyzed. This study was approved by the Ethics Committee of Shanxi Provincial Cancer Hospital.

Obtaining of cytology samples. In Group A, BWC was conducted in the suspicious malignant lung segments to obtain cytology samples; in Group B, after 15 ml of saline at 37°C was perfused in the suspicious malignant lung segments through a bronchoscope, 6 ml lavage fluid was recovered to obtain cytology samples; in Group C, a specially designed bending puncture needle was used to puncture the tissues of suspicious lesion to obtain tissues, and the obtained tissues were treated with pathological biopsy; at the same time, the residual tissues within the puncture needle were placed into an LCT tube to obtain cytology samples; in Group D, 2-4 pieces of lung tissues were taken through a pair of forceps from the suspicious malignant lung segments through a bronchoscope, and then placed and fixed in 10% formalin solution. Cytology samples were obtained after centrifugation at 3,000 x g, 4°C for 15 min and precipitation.

LCT method. Exfoliated cytology samples obtained by fiberoptic bronchoscopy were placed into a centrifuge tube with trypsin-EDTA solution. After shaking, the tube was kept on bench for 30 min. After gradient centrifugation at 400 x g, 4°C for 30 min, the cells were collected. Automatic cell preparation technique was used for tissue section preparation, and tissue sections were covered with optical gum and cover glasses after Papanicolaou staining (5,6).

Statistical methods. Sensitivity, specificity, positive and negative predictive values of LCT diagnosis were calculated according to pathological biopsy diagnoses. The conformity of the cytology diagnosis to the corresponding pathological biopsy in each group was estimated by κ coefficient using the Statistical Product and Service Solutions 19.0 analysis software (IBM Corp, Armonk, NY, USA). κ≥0.75 indicated excellent conformity; 0.4≤κ<0.75 indicated good conformity; κ<0.4 indicated poor conformity. ANOVA was used for the comparison of the rates among the four groups and Dunnett's test was the post hoc test used. P<0.05 indicated that the difference was statistically significant.

Results

General data of study subjects. A total of 901 patients who underwent fiberoptic bronchoscopy in Shanxi Provincial Cancer Hospital from June 2012 to June 2016 were selected in the present study. Among the patients 579 were males and 322 were females, with an average age of 56.2 years. There was no significant difference in age between males and females in this study (Tables I and II).

Results of fiberoptic bronchoscopy combined with LCT and pathology. In Group A (n=276), 214 patients received BWC combined with LCT, and there were 224 patients with positive pathological biopsy results, in which 193 cases were successfully detected with a κ-value of 0.426, indicating good conformity; in Group B (n=204), 162 patients received BAL combined with LCT, and there were 171 patients with positive pathological biopsy results, in which 149 patients were successfully detected with a κ-value of 0.430, indicating good conformity; in Group C (n=187), 151 patients underwent EBUS-TBNA combined with LCT, and there were 154 patients with positive pathological biopsy results, in which 146 patients were successfully detected with a κ-value of 0.769, indicating excellent conformity; in Group D (n=234), 188 patients underwent TBLB combined with LCT, and there were 192 patients with positive pathological biopsy results, in which 170 patients were successfully detected with a κ-value of 0.440, indicating good conformity (Table III).

Comparison of the sensitivity (detection rate) of fiberoptic bronchoscopy combined with LCT among the four groups. Detection rate of Group A was 86.17% (193/224), and the specificity was 59.62% (31/52); the detection rate of Group B was 87.13% (149/171), and the specificity was 60.61% (20/33); the detection rate of Group C was 94.81% (146/154), and the specificity was 84.85% (28/33); the detection rate of Group D was 88.54% (170/192), and the specificity was 57.14 (24/42). Comparing the detection rate of the four groups: Group C > Group D > Group B > Group A, and the detection rate of Group C was significantly higher than those of Groups A, B and D (P<0.05); there was no statistically significant difference in the detection rate among Groups A, B and D. Comparing the specificity of the four groups: Group C > Group B > Group A > Group D, and the specificity of Group C was significantly higher than those of Groups A, B and D (P<0.05); there was no statistically significant difference in specificity among Groups A, B and D (Tables IV and V).

Table I. Demographic characteristics of the patients.

Characteristics								Total	Average age (years)
Age (years)	20-30	31-40	41-50	51-60	61-70	71-80	81+		
Male	15	21	113	207	169	53	1	579	57.1±10.65
Female	9	20	66	121	80	24	2	322	55.2±11.35
Total	24	41	179	328	249	77	3	901	56.2±11.02

A total of 901 patients receiving fiberoptic bronchoscopy were selected in this study, including 579 males and 322 females.

Table II. Comparison of baseline data among the four groups [n (%)].

Items	Group A (n=276)	Group B (n=204)	Group C (n=187)	Group D (n=234)	t	P-value
Sex					0.930	0.818
Male	180 (65.22)	125 (61.27)	125 (66.84)	149 (63.68)		
Female	96 (34.78)	79 (38.73)	62 (33.16)	85 (36.32)		
Age (years)					7.676	0.053
<58	121 (43.84)	115 (56.38)	90 (48.13)	110 (47.01)		
≥58	155 (56.16)	89 (43.63)	97 (51.87)	124 (52.99)		
Smoking					0.295	0.961
Yes	98 (35.51)	68 (33.33)	63 (33.69)	80 (34.19)		
No	178 (64.49)	136 (66.67)	124 (66.31)	154 (65.81)		

Comparison of the incidence rates of complications/adverse reactions among four groups. In Group A (n=276), hemoptysis occurred in 1 patient, and the incidence of complications/adverse reactions was 0.36%; in Group B (n=204), tracheal injury occurred in 1 patient, and the incidence of complications/adverse reactions was 0.49%; in Group C (n=187), hemorrhage occurred in 1 patient, and the incidence rate of complications/adverse reactions was 0.53%; in Group D (n=234), pneumothorax occurred in 2 patients with a pneumothorax quantity of ~9.5%, and the incidence rate of complications/adverse reactions was 0.85%; the differences in the incidences of complications/adverse reactions among the four groups were not statistically significant (p>0.05) (Table VI).

Discussion

With the unacceptably high morbidity and mortality rates, lung cancer is one of the most common malignant tumors that endanger the lives and health of humans around the world. Cytology detection through fiberoptic bronchoscopy using cytology samples has become one of the most commonly used methods for the diagnosis of lung cancer. With the application of LCT technique, the accuracy of the diagnosis of lung cancer by cytology has been significantly improved. LCT also plays an important role in early diagnosis of lung cancer. In this study, clinical data from 901 patients with suspicious lung cancer who underwent fiberoptic bronchoscopy combined with LCT and pathological biopsy within the last four years were retrospectively analyzed and summarized. With histopathological diagnosis as gold standard, as well as the incidence rate of complications/adverse

Table III. Results of fiberoptic bronchoscopy combined with LCT and pathology as well as conformity (n, κ).

LCT	Pathological tissue		Total	κ-value
	Positive	Negative		
Group A (BWC)				
Positive	193	21	214	0.426
Negative	31	31	62	
Subtotal	224	52	276	
Group B (BAL)				
Positive	149	13	162	0.430
Negative	22	20	42	
Subtotal	171	33	204	
Group C (EBUS-TBNA)				
Positive	146	5	151	0.769
Negative	8	28	36	
Subtotal	154	33	187	
Group D (TBLB)				
Positive	170	18	188	0.440
Negative	22	24	46	
Subtotal	192	42	234	
Total	741	160	901	

LCT, liquid-based cytology test; BWC, bronchoscopic washing cultures; BAL, bronchoalveolar lavage; EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration; TBLB, transbronchial lung biopsy.

Table IV. Comparison of the detection rate of fiberoptic bronchoscopy combined with LCT among the four groups (%).

Fiberoptic bronchoscopy combined with LCT	Sensitivity[a]	Specificity	Positive predictive value	Negative predictive value	False positive rate	False negative rate
Group A (BWC)	86.17% (193/224)	59.62% (31/52)	90.19% (193/214)	50.00% (31/62)	40.38% (21/52)	13.84% (31/224)
Group B (BAL)	87.13% (149/171)	60.61% (20/33)	91.98% (149/162)	47.62% (20/42)	39.39% (13/33)	12.87% (22/171)
Group C (EBUS-TBNA)	94.81% (146/154)	84.85% (28/33)	96.69% (146/151)	77.78% (28/36)	15.15% (5/33)	5.19% (8/154)
Group D (TBLB)	88.54% (170/192)	57.14 (24/42)	90.43% (170/188)	52.17% (24/46)	42.86% (18/42)	11.46% (22/192)
χ^2	7.642	7.707	6.118	8.094	6.634	7.642
P-value	0.054	0.052	0.106	0.044	0.085	0.054

[a]Detected sensitivity/detection rate = the number of cases successfully diagnosed with lung cancer through pathology by fiberoptic bronchoscopy combined with LCT within the group/the number of cases pathologically diagnosed with lung cancer within the group x100%. LCT, liquid-based cytology test; BWC, bronchoscopic washing cultures; BAL, bronchoalveolar lavage; EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration; TBLB, transbronchial lung biopsy.

Table V. Comparison of false negative rate among the four groups.

Control group	χ^2	P-value
A (BWC)		
B (BAL)	0.079	0.778
C (EBUS-TBNA)	7.370	0.007
D (TBLB)	0.527	0.468
B (BAL)		
C (EBUS-TBNA)	5.690	0.017
D (TBLB)	0.168	0.682
C (EBUS-TBNA)		
D (TBLB)	4.234	0.040

BWC, bronchoscopic washing cultures; BAL, bronchoalveolar lavage; EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration; TBLB, transbronchial lung biopsy.

reactions, application values of bronchoscopy combined with LCT technique in the early diagnosis of lung cancer were evaluated.

In the present study, the sensitivity (detection rate), specificity and κ-value gained from the statistical data analysis of Group A/B/C/D were basically similar to those reported in previous studies (5,17,19). Sun *et al* (20) also revealed that EBUS-TBNA is the most advanced technique in the collection of cytology samples through microscopic examination. With EBUS-TBNA, tumor samples can be obtained that are not accessible by conventional techniques. Based on statistical analyses, it is not difficult to find that BWC/BAL/EBUS-TBNA/TBLB combined with LCT can reduce omission diagnose rate and misdiagnose rate of lung cancer, so they can be used as effective detection techniques for the early diagnosis of lung cancer. Fiberoptic bronchoscopy combined with LCT, as an important technique for early diagnosis of lung tumors, has the following advantages: i) simple operation, small trauma and high positive diagnosis rate; ii) few pneumothorax, hemorrhage, lung infection and other complications/adverse reactions; iii) avoidance of radiation from X-ray and computed tomography (CT)-guided percutaneous puncture biopsy/transmural biopsy to medical personnel and patients; and iv) less pain suffered by patients during operation, thus repeated examinations can be performed. In addition, the use of LCT fundamentally changes the traditional smear production methods and compensates their deficiencies. As a result, advantages of fiberoptic bronchoscopy combined with LCT are: i) access to cytology samples to the utmost possibility with less cell destruction; ii) maintenance of cytology samples to the utmost possibility during smear process; and iii) single-layer uniformly distributed smears and concentrated cells with clear structures, which are conducive to better radiograph reading experience.

Regarding the false positive cases in each group, there were 57 cases of false positive cases of liquid-based cytology in the four groups. Histopathological examinations diagnosed those cases as tuberculosis, hamartoma, and lung abscesses and other inflammatory infections. Cytological diagnosis is mainly based on heteromorphism of cells and nucleus morphology. Abnormal cell shape is often used as an important basis for diagnosing malignant transformation. Changes in proliferation, metaplasia, and degeneration of lung cells that occur during inflammatory infections may lead to varying degrees of morphological changes, which in turn affect the diagnosis and lead to the false positive diagnosis. In addition, the appearance of tumor without obvious malignant features and well-differentiated tumor has similarities with hyperplastic cells, which is another cause of false positive diagnosis. Fernández-Bussy *et al* (21) also reported that the application of pulmonary lesions cytology and biopsy may misidentify malignant cells, resulting in false positive and false negative diagnosis. Therefore, repeated examinations and combination of imaging techniques are needed to improve the diagnosis.

Table VI. Comparison of the incidence rates of complications/adverse reactions among the four groups.

Group	Hemorrhage/ hemoptysis	Hemothorax	Pneumothorax	Lung infection	Tracheal injury/spasm	Hyoxemia	Arrhythmia/ heart failure	Total n (%)
Group A (n=276)	1	0	0	0	0	0	0	1 (0.36)
Group B (n=204)	0	0	0	0	1	0	0	1 (0.49)
Group C (n=187)	1	0	0	0	0	0	0	1 (0.53)
Group D (n=234)	0	0	2	0	0	0	0	2 (0.85)
χ^2	2.046		5.741		3.618			0.583
P-value	0.563		0.126		0.306			0.900

Besides, normal tissues may be collected by bronchoscopy under direct vision, which in turn leads to false negative cases. However, the application of EBUS-TBNA technology in Group C is a good way to solve this defect because it can be used to obtain cytological samples under visible conditions, leading to the lowest false negative rate among the four groups.

It is known that collection of tissue samples by fiberoptic bronchoscopy may lead to various complications or adverse reactions (21). However, in this study, the incidence of complications/adverse reactions in Group A/B/C/D was low, and there were no statistically significant differences in incidences of complications/adverse reactions among the four groups, which is consistent with the findings reported by Chan *et al* (22) and Asano *et al* (23). Although pneumothorax occurred in 2 patients in Group D (n=234), pneumothorax quantity was only 9.5%. Patients combined with pneumothorax were able to conduct self-absorption without treatment. It has been reported (24) that the incidence rate of pneumothorax was 10-40% and that of hemoptysis was 20-33% after CT-guided percutaneous puncture biopsy. However, the incidence of pneumothorax and hemoptysis of patients in this study were significantly lower than those of patients who received percutaneous biopsy, possibly due to the small trauma and simple operation. Incidence of lung cancer is significantly increased with aging (25). Silvestri *et al* (26) showed that the safety of performing bronchoscopy under sodium-fluorophosphate anesthesia for aged population is comparable to that of young individuals. Therefore, the combination of BWC/BAL/EBUS-TBNA/TBLB and LCT is also safe for aged population.

Since histopathological diagnosis is the gold standard for the diagnosis of lung cancer and lung cancer classification, cytology diagnosis cannot be used to guide the treatment. All patients included in this study were pathologically diagnosed by bronchoscopic biopsy, while patients only diagnosed by bronchoscopy combined with liquid-based cytology were not included, which is a shortcoming of this study. However, tissue contamination and missed labeling may lead to misdiagnosis of histopathological examination. Therefore, repeated diagnosis or combination with clinical manifestations and imaging examination is also necessary to achieve accurate diagnosis.

In summary, the four methods (BWC/BAL/EBUS-TBNA/TBLB) combined with LCT are safe and reliable techniques for the early diagnosis of lung cancer. However, the combination of EBUS-TBNA and LCT is the most promising one. LCT technique cannot completely replace conventional histopathological biopsy, but LCT is indispensable for the diagnosis of early-stage lung cancer due to the difficulties in tissue collection through conventional methods. Therefore, combining the two methods can improve the early diagnosis of lung cancer.

Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

SH conceived, designed the study and drafted the manuscript. SH, WY and HL collected, analyzed, and interpreted the patient data, and revised the manuscript critically for important intellectual content. All authors read and approved the manuscript and agree to be accountable for all aspects of the research in ensuring that the accuracy or integrity of any part of the study are appropriately investigated and resolved.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Shanxi Provincial Cancer Hospital (Taiyuan, China). Signed informed consents were obtained from the patients or the guardians.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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