Am J Transl Res 2021;13(7):7775-7782
www.ajtr.org /ISSN:1943-8141/AJTR0131672

Original Article

Autofluorescence bronchoscope diagnosis for lung nodules and masses

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Received February 8, 2021; Accepted February 25, 2021; Epub July 15, 2021; Published July 30, 2021

Abstract: Objective: This study set out to enhance the positive detection rate of lung tumors, diagnosis of nodular lesions and improve the accuracy of lung cancer classification by evaluating the clinical value of autofluorescence bronchoscopy (AFB). Methods: Forceps biopsy, brush biopsy, needle aspiration, and washing techniques were performed alone and in combination with AFB among 38 subjects who were analyzed cytologically and histologically. Results: Our results showed that 33 out of 38 patients were diagnosed with lung cancer, with an overall positive diagnostic rate of 86.8% when the combined methods and AFB was performed; the positive diagnostic rates obtained by forceps, needle aspiration, brush biopsy and washing methods were 68.4%, 84.2%, 55.3% and 36.8%, respectively. Compared to the overall positive rate, the positive diagnostic rates detected by forceps and needle aspiration were not statistically significant ($P>0.05$). However, the positive rates gained by the brush biopsy and washing method were statistically significant ($P<0.01$). In addition, we compared the 38 cases evaluated with AFB and 43 cases evaluated with "traditional" white light bronchoscopy (WLB), using the same methods. Conclusions: AFB and WLB markedly improved the positive diagnosis rate when combined with forceps and needle aspiration. The overall positive diagnostic rate of lung cancer scanned by WLB was increased from 60.5% to 86.8% ($P<0.01$) by using the combined methods of forceps, brush biopsy, needle aspiration and washing. Moreover, the accuracy of lung cancer classification combined with cytology and cell immunohistochemistry was improved. These results showed that a variety of inspection techniques and diagnostic technologies effectively play a complementary role in the diagnosis and classification of lung cancer.

Keywords: Autofluorescence bronchoscopy, AFB, WLB, lung cancer, immunocytochemistry

Introduction

Bronchoscopy is a preferred method in the diagnosis of lung cancer. It is commonly used in living tissue sampling to determine the malignant extent of lung cancer. Diagnostic techniques for cancer typically consist of forceps biopsy, aspiration, needle aspiration cytology and brush biopsy [1]. However, the innovation of fiberoptic bronchoscopy has evolved as micro technology develops, and video bronchoscope has been put into use with the development of imaging technology. Recently, the use of AFB, narrow band imaging (NBI) and linear endobronchial ultrasound (EBUS) are applied in clinical practice [2].

Compared with WLB, AFB may increase the diagnostic rate of the early tracheal mucosa cancer, so we employed the combined methods of forceps, brush biopsy, needle aspiration and washing in the inspection of lung cancer. For samples with unknown cytology and classification, we examined them using a combination of cytology and cell immunohistochemistry. The results showed that the classification of lung cancer cell type was improved. We analyzed 38 cases, by using forceps biopsy, needle aspiration, brush biopsy and washing methods in our hospital from October 2018 to December 2019. In addition before September 2019, 43 patients were examined with WLB typically consisting of

forceps biopsy, aspiration, needle aspiration cytology and brush biopsy [1].

Materials and methods

Clinical data

From October 2018 to December 2019, 38 patients who were checked with bronchoscopy after the clinical and radiological examination in Jinan Central hospital, were biopsied with a variety of methods of forceps, brush biopsy, needle aspiration and washing. There were 22 males with an age range of 27 to 82 years old, with 58 years old as the average age and 8 females with an age range of 23 to 77 years old, with an average of 48 were evaluated. For evaluation of the clinical effect of AFB, 43 patients, who had been examined by the same methods but with WLB in our hospital before September 2019, were selected as the control group. This study was approved by the Medical Ethics Committee of Shandong Provincial Qianfoshan Hospital (Approved No. YXLL-KY-2018073).

Methods and apparatus

The equipment used consisted of a Japanese OLYMPUS BF-F260 AFB and OLYMPUS BF260 WLB. Briefly, after conventional local anesthesia, the WLB was inserted through the nose or mouth to analyze the trachea and bronchi in order to determine the location of the tumor based on the lung CT and chest X-ray examination. In order to switch the WLB to AFB once an abnormal condition was found, a special needle was sent to the tissue mass wall via the trachea and bronchus, the tip of the needle was 5-10 mm from the end of bronchoscope, and then the needle was put into the diseased tissue seen on the dark red fluorescent images and was suctioned with a 20 ml syringe for about 20 s and this action was repeated 2-3 times. The needle was then pulled out. The sample specimine was then pushed on a slide gently and smeared on 4-5 sheets (one of 1-2 sheets would be used in Immunocytochemistry). Local bleeding was treated with 1/1000 adrenaline, a special biopsy forceps was used with on lesions with 2-3 blocks. The bleeding was first stopped with thrombin, then we performed a brush biopsy operation; afterwards, the pipline was washed with saline and we kept the fluid as the specimen. Finally, four kinds of samples were checked by cytology and histology. Typical AFB images were shown in **Figure 1**.

Diagnostic criteria

Smear cytology had three levels: negative (cells had no atypia), abnormal (cells had some atypia, but the number was still not clear enough) and malignant (cell atypia was diagnosed as malignant). All test results were divided into two types: positive and negative. If the malignant cell type was difficult to smear, the possibility of lymphoma can be excluded with reference to the histological diagnosis of forceps, and (or) by immunocytochemistry (squamous cell carcinoma of CK5/6(+); adenocarcinoma CK8/18(+); small cell undifferentiated carcinoma Syn (+) and Cga (+), etc.) and staining (Wright stained). Samples shown in (**Figure 3**, Cases 1-3).

Statistics

Statistical analysis was performed using GraphPad Prism 7.0 and SPSS 22.0. Enumeration data were presented as rate (%), and χ^2 test was used. $P<0.05$ indicated a statistically significant difference.

Results

The diagnostic result with the variety of drawing methods

The results showed that 33 out of 38 patients were diagnosed as positive by combining the common applications of AFB, forceps, needle aspiration, brush biopsy and washing method. The combined methods led to an overall diagnostic rate was 86.8%, whereby using one of the methods of forceps, needle aspiration, brush biopsy or washing obtained the diagnostic rates of 68.4%, 84.2%, 55.3% and 36.8%, respectively. The positive diagnosis rate of forceps and needle aspiration were compared with the overall detection rate and was found to be not statistically significant ($P>0.05$). However, the brush biopsy and washing method had a statistical significance ($P<0.01$). These results showed that using the combined drawing methods was superior to using just one type of methods. As shown in **Figure 2**.

Results of combining methods with AFB

The application of different methods showing positive diagnosis rates are illustrated in **Figure**

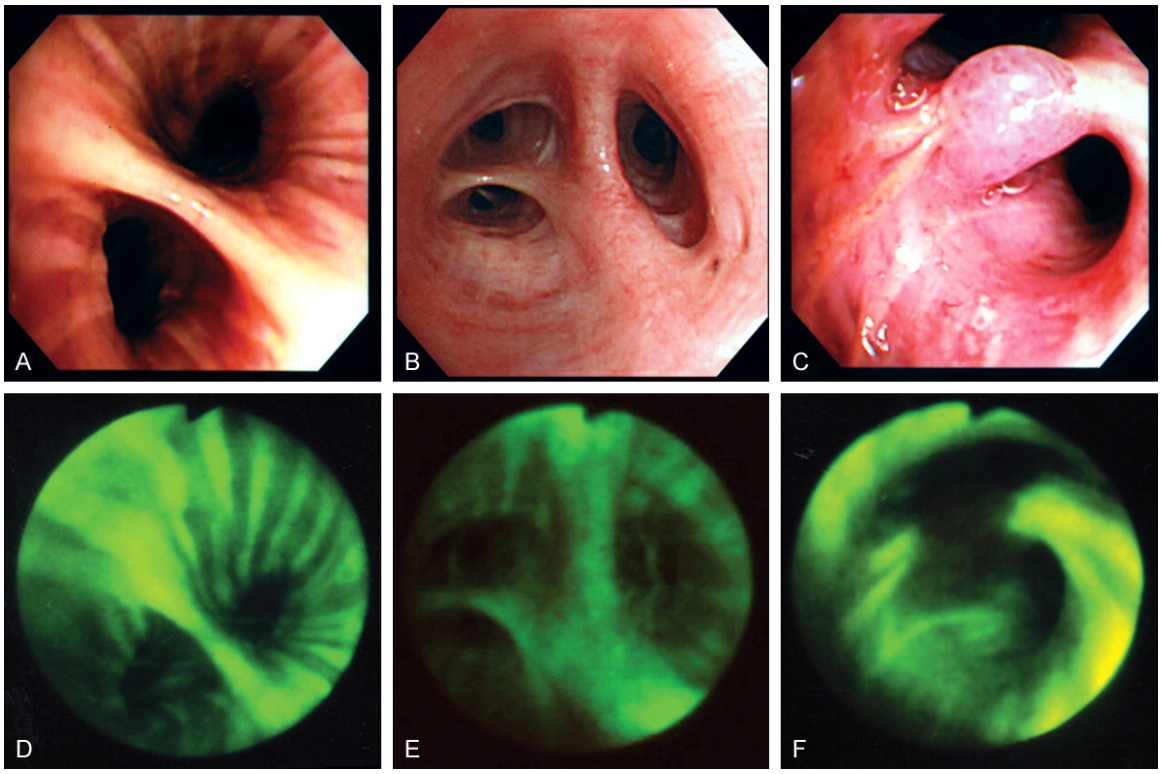

Figure 1. Comparison of image of WLB and AFB (A) and (D) showed normal appearance with WLB and abnormal lesion with AFB respectively, at the same site. (B) and (E) showed abnormal appearance at WLB and suspicious lesion at AFB respectively, at the same site. (C) and (F) showed suspicious lesions at both WLB and AFB respectively, at the same site.

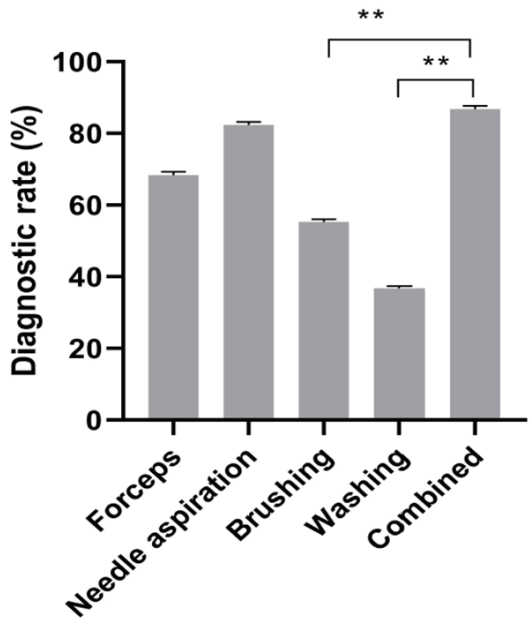

Figure 2. The diagnostic result with the variety of drawing methods. **P<0.01.

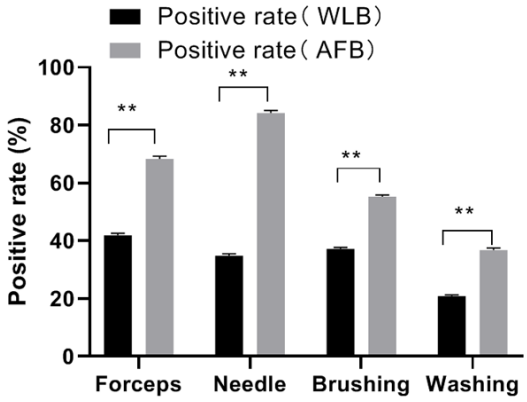

Figure 3. Results of combining methods with AFB. **P<0.01.

2. With the application of AFB to forceps (68.4%, P<0.05), needle aspiration (84.2, P< 0.01) positive diagnosis was markedly improv ed, but brush biopsy and washing method displayed no statistically significance (P>0.05). Compared with WLB, AFB had more impact on

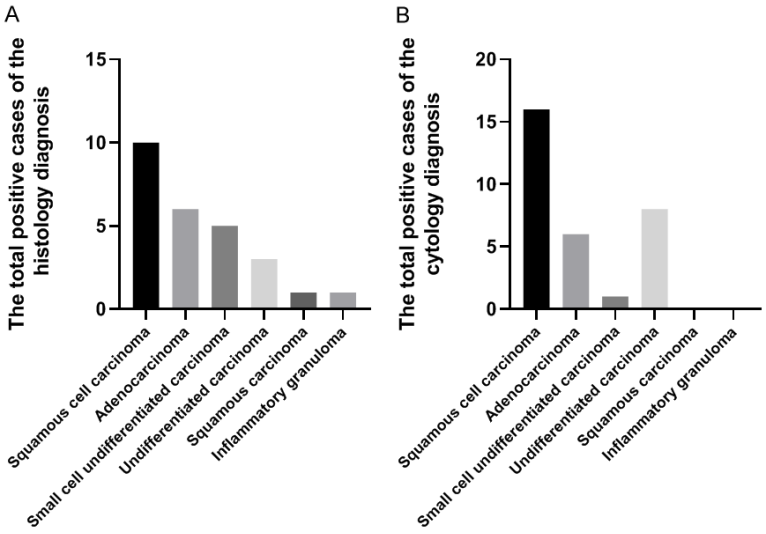

Figure 4. The total positive cases of the (A) histology diagnosis and (B) cytology diagnosis.

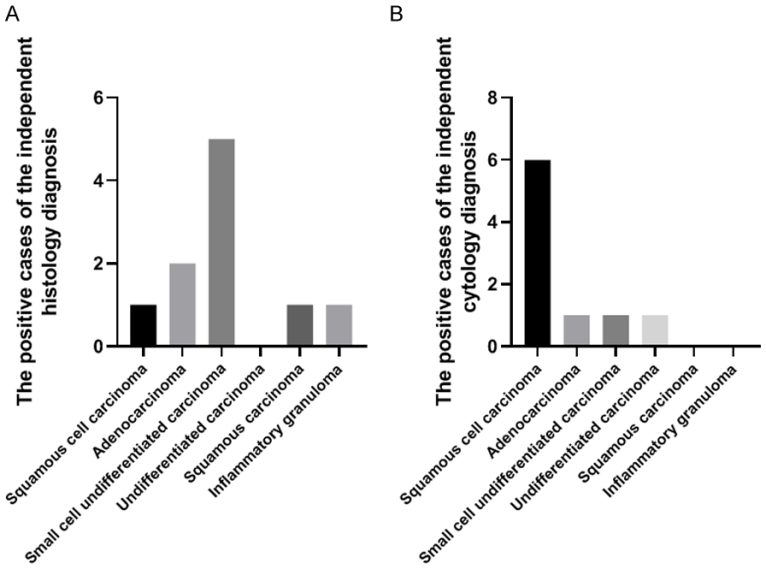

Figure 5. The total positive cases of the (A) independent histology diagnosis (B) independent cytology diagnosis.

the results of forceps and needle aspiration, with the positive diagnostic rate increasing, and the combined rate of positive diagnosis increased from 60.5% to 86.8% ($P<0.01$); but the results of brush biopsy and washing were less effective. As shown in **Figure 3**.

The total positive cases of histology or cytology diagnosis

There were 32 cases of lung cancer and one case of inflammatory granuloma in 33 patients, which had been tested by histology and cytology. The total positive rate of the histology diagnosis was 78.8% (26/33). The total positive rate of the cytology diagnosis was 93.9% (31/33). The positive rate of the independent histology diagnosis was 30.3% (10/33). The positive rate of the independent cytology diagnosis was 27.3% (9/33). The positive rate of the common diagnosis of the histology and cytology was 42.4%. The positive diagnosis from the histology and cytology in tumor type had the same important value in the examination of the lung mass or nodule compared with the bronchoscopy. They played a complementary role effectively. There were 38 patients, who were diagnosed, as shown in **Figures 4**-**6** and **Table 1**.

Discussion

Bronchial needle aspiration biopsy forceps had a higher diagnostic value

Bronchoscopic biopsy has always been the diagnostic criteria for bronchial carcinoma [3]. For Tthe diagnosis of exogenous tumors, biopsy forceps with the standard bronchoscope is easier, but the tumor of the bronchial surroundings or submucosa is more difficult to be diagnosed [4]. This is because the submucosal tissue with infiltration is more rigid, so that the biopsy forceps in application of peribronchial tumor extraction or sampeling cannot be applied widely [5]. When the biopsy samples cannot be identified, the bronchial brush biopsy can be used. The infiltration of submucosal tumors and the external pressure of bronchial cancer by conventional forceps biopsy is undesirable. This is partly due to the difficulty of the biopsy, or that the mass is too deep to reach for conventional forceps biopsy. When this situation

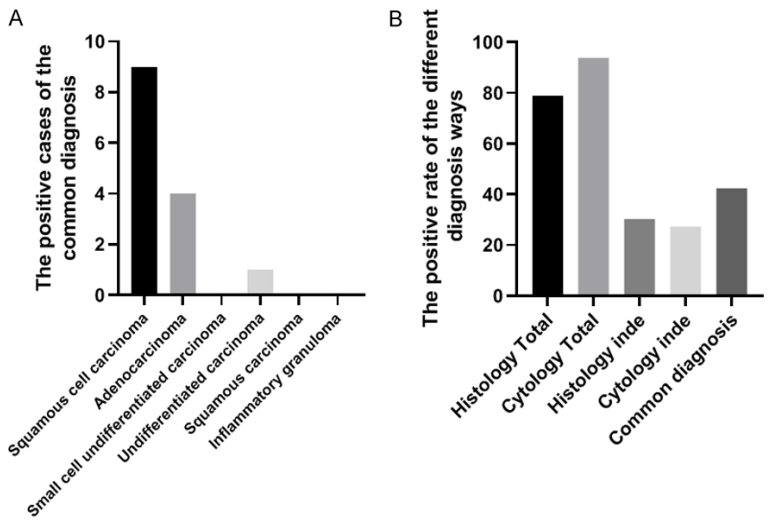

Figure 6. Effect of different diagnosis methods. A. The positive cases of the common diagnosis. B. The positive rate of the different diagnosis ways.

arises, the bronchial needle aspiration biopsy forceps technique has a higher diagnostic rate [5].

Using needle aspiration can cause less bleeding than using forceps for biopsy and brush biopsy, because it is more suitable for necrotizing live submucosal lesions. It is unnecessary for needle aspiration to be used on the surface of necrotic tissue and it does not have to be repeated on normal mucosa. It can directly access into the dynamic organization. Some researchers have observed that the bleeding from needle aspiration biopsy is less than that of the forceps biopsy [5, 6]. Therefore transbronchial needle aspiration is a safe method which can significantly improve the fiber bronchoscopy samples aqured in the peribronchial or submucosal invasive diagnosis of bronchial cancer rates than with single forceps biopsy.

Combination of different techniques had a high diagnosis rate

Compared with common diagnosis in 33 cases, the diagnosis rate obtained from the study of 38 patients by forceps, needle aspiration, brush biopsy and washing examination was 86.8% overall, whereas the diagnostic rates of forceps, needle aspiration, brush biopsy and washing method were respectively 68.4%, 84.2%, 55.3% and 36.8% (**Figure 1**, P<0.01). The positive diagnosis rate of needle aspiration, had no statistical significance (P> 0.05), while brush biopsy and rinsing had statistical significance (P<0.01). Studies have shown that bronchial needle aspiration is a powerful way in the diagnosis of malignant endobronchial lesions [8]. Combined with transbronchial needle aspiration, bronchial biopsy, brush biopsy and washing method the diagnosis rate ranged from 46% to 70% (P<0.05), with no obvious complications such as pneumothorax or bleeding. They has also been a reportedcase with benign tumor (aspergillosis), by bronchial biopsy [9].

In 38 patients, there was also no negative cases tested by transbronchial needle aspiration and positive ones tested by bronchial biopsy, and only one case of benign lesions (granulomatous inflammation) was detected by forceps biopsy. Bronchial needle aspiration only showed “non-malignant” types and could not determine the nature of disease.

Some existing findings show that a single method diagnosis leads to diagnostic yields of less than 80%. However, a combination of all of the methods can improve the diagnostic rates up to 93.4%. These results suggest that the diagnosis of lung cancer with a combination of techniques plays a complementary role [7].

Bronchial lavage cytology has less priority in malignancy diagnosis

Bronchial lavage samples are collected from the lung tissue distal to the bronchial fluid; and bronchial lavage specimens are usually collected from the airways, bronchial, and not from the alveoli [2]. The best way of getting the sampling is by bronchial lung biopsy, transbronchial needle aspiration and brush biopsy. Diagnosis of malignancy of bronchial lavage cytology is unnecessary. For any patient, bronchial washing fluid has never tested positive [10]. However, bronchial washing fluid can be first detected for the K-ras positive gene (a biomarker of lung cancer), which can be used for diagnosis [11].

Table 1. 38 cases of patients with diagnosis of AFB tracking

Diagnosis	Cases (+)	Cases (-)	Tracking
Squamous cell carcinoma	16	1	Smearing: G+-bac.
Adenocarcinoma	7	1	Operation: Adenocarcinoma
Small-cell undifferentiated carcinoma	6	1	Operation: Inflammatory granuloma
Squamous carcinoma	1	1	Smearing: TB
Undifferen-tiated carcinoma*	1, Operation: Adenocarcinoma	1	Sputum: Adenocarcinoma
Undifferen-tiated carcinoma**	1, Operation: Pulmonary lymphoma		
Inflammatory granuloma	1, Sarcoi-dosis		

*Independent cytology; **The same histological and cytological diagnosis.

AFB is an important part in malignancy diagnosis

AFB is a new bronchoscopic technique which was developed by using cell spontaneous fluorescence techniques and computer image analysis techniques. With AFB contrasting white light and fluorescence can be used under the same dual image, normal tissue has green fluorescence images, and a fluorescence decrease is caused by hypertrophicmucosa of the tumor lesions which has taken on a dark red fluorescence in images. AFB can also be compared with white light and fluorescence imaging in a dual-screen at the same time. The normal tissue is green in the fluorescence image. Neoplastic lesions are represented as red dark images due to hypertrophy mucosal decreasing the fluorescence. It improves the ability to identify tumor lesions, help detecting early lesions and determining the lesion focus, thus guiding clinical treatment.

In a study conducted by Haussing, 1,173 patients were evaluated and the results showed that AFB improved the diagnosis rate of Phase II to Phase III dysplasia (P=0.03), but had a low diagnostic rate for detecting casinoma foci, compared to "traditional" WLB [12]. Autofluorescence endoscopy could not distinguish preinvasive lesions and other changes of benign epithelial cells very well, such as bronchitis; thus patient's sputum cells often showed suspicious malignant or malignant features which could not be identified by the instruments [13]. It is necessary to identify the color of preinvasive disease and bronchitis for improving the specificity. AFB allows rapid scanning of large areas of the bronchial surface for subtle abnormalities that are not visible to white-light exam. However, some researchers claim that periodic follow-up with WLB and AFB showed no evidence of progression in the preneoplastic lesions [14].

Our findings shown in **Figure 2** were that the joint diagnosis rate of AFB rose from 60.5% to 86.8% (P<0.01). It significantly and effectively improved the early detection and diagnosis of lung cancer. The possible reason might be that the blood flow around precancerous lesions or cancerous cells increases which was detected by the fluorescence expression, thus improving the positive detection rate. However, bleeding and inflammation on the mucosal surface could affect the results, leading to false positives [15].

Liquid-based cytology test is an important adjunct to cell typing diagnosis for the TCT bronchoscopy brush biopsy

As shown in **Figure 3**, the lumps or nodules in the lung were examined by bronchoscopy, the positive diagnosis and tumor type in the histology and cytology has important value, both have an effective complementary role. The positive histological diagnosis was 78.8% (26/33), total positive cytology was 93.9% (31/33); independent histological diagnosis was 30.3% (10/33), the independent cytology diagnosis was 27.3% (9/33), the diagnosis of histological and cytological exam was the same 42.4%, which was similar with others studies' findings of the cytological diagnosis and pathological diagnosis of tumor resection [16]. It is well known that the diagnosis of cancer is much easier than diagnosis of individual cell types [19].

In 33 positive cases, 3 cases had undifferentiated carcinoma by the histological diagnosis due to the fact that the sample was too small to obtain enough tissue to confirm the diagno-

sis. Among 2 cases with cytological diagnosis (1 had squamous cell carcinoma and 1 adenocarcinoma), 1 case was diagnosed as primary pulmonary lymphoma after surgery; 8 cases were diagnosed as undifferentiated carcinoma cytology, among which 6 were typed by the histological diagnosis (4 had small cell undifferentiated carcinoma, 1 squamous cell carcinoma and adenocarcinoma, which was confirmed as adenocarcinoma after operation). The other cases had the same diagnosis with histological and cytological inspection and the post-operative diagnosis was primary pulmonary lymphoma. The characteristics of poorly differentiated cancer are not obvious. It was difficult to identify types of cancer according to morphology alone. The combination of cytology and immunocytochemistry can increase the sensitivity of typing diagnosis [17]. However, the lack of samples is a problem to examination of both immunocytochemistry and cytology. Yang Yan [17] solved the problem of small samples by the liquid-based cytology test (Thinprep cytological test, TCT). They combined CKl0/13, CK7, CKl8, CD56 and SYN detection and cell morphology as the basis of cell typing diagnosis of lung cancer. It improved accuracy of diagnosis and might become an important adjunct to cell typing diagnosis for the TCT bronchoscopy brush biopsy.Currently, LCT is a technology of superior quality among exfoliated cytology examination techniques, for that it avoids the disadvantages of traditional smear methods, by removing too much blood and mucus and reduces overlapping cells. Treated with LCT, slides can be biochemically examined simultaneously with immunohistochemistry and polymerase chain reaction, thus preserving specimens for appointment. Therefore, it has more advantages in diagnosis of lung cancer [18].

EBUS was an effective method for special circumstances

As shown in **Table 1**, among 5 negative cases which were tested by bronchoscopy, 3 cases were diagnosed by smear bacteria and sputum cancer cell check, and 2 patients were not tested by the minimally invasive diagnostic techniques with a clear diagnosis following surgeries. When suspicious lesions were found in the chest radiology check, minimally invasive diagnostic techniques are required if conventional bronchoscopy and CT-mediated fine-needle aspiration still cannot provide a confirmed diagnosis. The current study showed that EBUS is a safe method [19]. EBUS can be employed as a further check for those patients who cannot be diagnosed by the examination of conventional bronchoscopy and CT. Nevertheless, we claim that if some patients still cannot be diagnosed by EBUS, they need to have further invasive examination [20]. In these cases, mediastinoscopy or thoracotomy is also necessary to explore the determining nature of tumors [21].

In recent years, studies have confirmed that fluorescent bronchoscopy can effectively improve the detection rate of early malignant lesions in the airway, especially cancer in the bronchial epithelium. Based on this, the present study justified the value of AFB in diagnosing lung cancer and evaluated its role in pathological typing. However, the application of this technique was limited to a small number of cases, the diagnosis of precancerous lesions and carcinoma should to be continually studied in the future.

To date, bronchoscopy has become an effective method for the diagnosis and treatment of lung cancer. With the latest techniques available, we can improve the diagnosis and staging of our patients.

Acknowledgements

We acknowledge the contribution of Ms. Suzan McNamara (PhD) to the article for ideas.

Disclosure of conflict of interest

None.

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