Int J Clin Exp Pathol 2016;9(5):5575-5581
www.ijcep.com /ISSN:1936-2625/IJCEP0023796

Original Article

Comparison of smear cytology with histopathology in the ultrasonography-or computed tomography-guided biopsy of lung neoplasms

Fei Yang[1*], An Su[5*], Qiongrong Chen[1], Weipeng Yan[3], Ling Yang[2], Jianguo Huang[4], Yulin Liu[3], Jing Zhang[2], Yanping Hu[2]

Departments of [1]Pathology, [2]Medical Oncology, [3]Radiology, [4]Ultrasonography, Hubei Cancer Hospital, Wuhan, Hubei, China; [5]Department of Medical Oncology, Zhongshan Hospital of Xiamen University, Xiamen, Fujian, China. [*]Equal contributors.

Received January 11, 2016; Accepted March 23, 2016; Epub May 1, 2016; Published May 15, 2016

Abstract: The significance of smear cytology of ultrasonography (US) or computed tomography (CT) guided core needle biopsy tissues have never been referred to. In this study, the first comparison between cytology and the corresponding histopathology was made to clarify the role of additional smear cytology in the diagnosis of lung lesions. This was a retrospective analysis of sixty-nine consecutive patients of clinically diagnosed lung neoplasm who received the examinations of smear cytology and histopathology in the same biopsy tissue guided by US or CT between April 2014 and June 2015. The overall consistent rate for smear cytology and histopathology results was 69.57% (48/69). The diagnosis rate of lung cancer was 53.62% (37/69) for smear cytology and 66.67% (46/69) for the corresponding histopathology (P = 0.118). Although 9 (13.04%) more cases were diagnosed as lung cancer by histopathology, 4 cases (5.80%) were diagnosed as lung cancer by smear cytology, not by histopathology. Smear cytology and histopathology shared the same pathological classification rate (89.19%) in patients with malignancy. The consistent rate of lung cancer subtypes for smear cytology and histopathology was 56.76% (21/37). Smear cytology of US or CT guided core needle biopsy tissue is a simple and cost effective diagnosis method, which shows a quick diagnosis and a good correlation with histopathology on lung cancer, and also enhances accuracy of histopathology. It is recommended as a routine cytology examination in case of core needle biopsy in lung tumor.

Keywords: Smear cytology, histopathology, ultrasonography, computed tomography, lung biopsy

Introduction

Lung cancer is still one of the leading causes of cancer-related deaths all over the world. In developing countries, many patients were in the locally advanced or advanced stage at initial diagnosis. Some of them can have a definitive diagnosis by pleural effusion cytology, bronchoscopy and superficial lymph node biopsy. Nevertheless, many patients remain undetermined after initial evaluation.

Imaging-guided percutaneous transthoracic biopsy is an effective, safe and minimally invasive technique which obtains tissue specimens from lung lesions [1], the result of which can be conductive to diagnosis and provision of enough samples for somatic mutation analysis [2]. Computed tomography (CT) and ultrasonography (US) are two major types of guidance methods. Compared with US guidance, CT guidance showed longer procedure duration and higher complication rate. This is because CT cannot generally provide the real-time monitoring of both needle movement and lesion displacement with respiration [1]. However, US guidance is only applied to subpleural lung nodules or lesions that have a contact with pleural [3]. In spite of advantages and disadvantages of these two methods, they show a similar diagnosis success rate (more than 85%) [1, 4, 5].

In clinic, many patients with lung lesions still fail to be correctly diagnosed by CT or US guided core needle biopsy. Even if a correct diagnosis can be made in most patients, it can take two

Table 1. Characteristics of the patients presented with clinically lung tumor

Characteristic	n (%)
Age (Median)	59 (range: 36-81)
Gender	
Male	41 (59.42)
Female	28 (40.58)
Presenting complaint	
Chest pain	15 (21.74)
Cough	28 (40.58)
Hemoptysis	5 (7.25)
Fever	3 (4.35)
Low back pain	4 (5.80)
No symptoms	12 (17.39)
Others	2 (2.90)
Tumor size	
< 3 cm	22 (31.88)
3-7 cm	43 (62.32)
≥ 7 cm	4 (5.80)
Tumor location	
Peripheral	66 (95.65)
Central	3 (4.35)
Smoking	
Yes	36 (52.17)
No.	33 (47.83)
Guidance methods	
CT	55 (79.71)
US	14 (20.29)
Diagnosis	
Lung cancer*	50 (72.46)
Tuberculosis	1 (1.45)
Undetermined	18 (26.09)

Abbreviation: CT, computed tomography. US, ultrasonography. *: 1 case was diagnosed as lung metastasis by further examinations.

Table 2. Summary of results of smear cytology and histopathology

	Negative	Atypical	Malignant	*P* value
Smear cytology	25	7	37	0.276
Histopathology	17*	6	46	

*: 1 case was diagnosed as tuberculosis by ultrasonography guided biopsy.

or three days for the histopathology result to come. So it will be meaningful to further improve the diagnosis success rate and shorten the diagnosis duration for imaging-guided transthoracic biopsy. As such, we examined smear cytology in the CT or US guided core needle biopsy tissue specimens, and made the first comparison between cytology and the corresponding histopathology in order to clarify the significance of additional smear cytology in this condition.

Materials and methods

Patient selection

This was a retrospective analysis of sixty-nine consecutive patients of clinically diagnosed lung neoplasm who received the examinations of smear cytology and histopathology in the same biopsy tissue guided by the US or CT between April 2014 and June 2015. This study was approved by the Ethics Committee in Hubei Cancer Hospital. And a written informed consent was obtained from each patient before biopsy.

All patients were evaluated by thorough clinical examination followed by routine investigations including complete blood count, serum biochemistry, contrast-enhanced chest CT, US or CT of abdomen and pelvis.

CT and US guided biopsy

CT procedures were performed in the 128-slice spiral CT (SOMATOM Definition AS; Siemens Medical Solutions, Forchheim, Germany) in the Department of Radiology, and US procedures were conducted in a US system (LOGIQ E9; GE Medical Systems, Milwaukee, Wis, America) in the Department of US. The body position of patients depended on the location of the lesion to obtain the most direct route for biopsy. The skin entry site was marked by using the laser light from the CT gantry for the former guidance and by the appropriate route to the lesion under the real-time visualization for the latter guidance. All tumor tissues were acquired by using an 18-gauge needle containing a 23-mm specimen notch at the tip (Pro·Mag™; Medical Device Technologies, Inc., Gainesville, Fl, America). One or two 23-mm-long core specimens were obtained for CT guidance, and two to four 23-mm-long core specimens were obtained for US guidance in each procedure. For each biopsy, the surface (a very small amount of liquid or bloody substances) of the specimen was gently smeared on a glass slide without extruding the tissue, which then was sent for cytology exami-

Table 3. Comparison of smear cytology with histopathology under the US guided biopsy (n = 14)

Smear cytology	Histopathology			Consistent numbers
	Negative	Atypical	Malignant	
Negative (n = 9)	5	0	4	5
Atypical (n = 0)	-	-	-	-
Malignant (n = 5)	1	0	4	1

Abbreviation: US, ultrasonography.

Table 4. Comparison of smear cytology with histopathology under the CT guided biopsy (n = 55)

Smear cytology	Histopathology			Consistent numbers
	Negative	Atypical	Malignant	
Negative (n = 16)	10	1	5	10
Atypical (n = 7)	0	3	4	3
Malignant (n = 32)	1	2	29	29

Abbreviation: CT, computed tomography.

nation by Baso Liu's stain [6]. The result was reported in about 10 minutes. After finishing the smear, each specimen was placed in formaldehyde-filled sterile containers that were used to make paraffin tissue sections and submit for histopathology diagnosis. Generally, the diagnosis time for histopathology was about three days.

Pathological results and follow-up

Smear cytology and histopathology yielded 4 possible results: (1) malignant (almost all were lung cancer); (2) atypical (suspicious for malignancy); (3) benign; (4) non-diagnostic. Due to the relative diagnosis limitation of cytology and core biopsy tissue on the benign disease, the benign and non- diagnostic results were taken as negative results except a definitive diagnosis such as tuberculosis. The atypical and negative results were taken as undetermined diagnosis.

After the completion of initial evaluation, patients were followed-up by their oncologists in the outpatient department or by telephone. The follow-up interval was based on the regular standard of two or three months.

Statistical analysis

Simple descriptive statistics were used to report general clinical information and pathological results. The results of smear cytology and histopathology were compared using the chi-squared test where appropriate. Sensitivity, specificity, and accuracy were not calculated in virtue of lack of surgery pathology (golden criteria for pathological diagnosis). A two-sided P value < 0.05 was considered statistically significant. All statistical analyses were performed using PASW statistics 18.0 software (Apache Software Foundation, Forest Hill, Md).

Results

Patient characteristics

A total of 69 patients with smear cytology and histopathology were identified (**Table 1**). 41 patients were male and 28 patients were female. Age of the patients ranged from 36 to 81 years with a median age of 59 years. Cough (n = 28) and chest pain (n = 15) were the common presentation. Additionally, lung tumors were found in the regular medical examination for 12 patients. The tumor size was less than 3 cm in 22 patients and more than 7cm in 4 patients, and it ranged from 3 cm to 7 cm in the 43 patients. Nearly all female patients had no history of smoking, and most male patients had a heavy smoking history.

The CT guidance biopsy was made on 55 patients and the US guidance biopsy was conducted on 14 patients. The initial pathological examination revealed 49 cases as primary lung cancer, 1 case as lung metastasis, 1 case as lung tuberculosis, and 18 cases as undetermined diagnosis.

Comparison of smear cytology and histopathology

Smear cytology showed 37 cases were lung cancer, 7 cases were atypical lesion, and 25 cases with negative diagnosis. For histopathology, 46 cases were diagnosed as lung cancer, 6 cases were diagnosed as atypical lesion, 17 cases showed negative diagnosis (**Table 2**).

For US guided biopsy (n = 14), smear cytology indicated 5 cases had a diagnosis of lung cancer (corresponding histopathology: 4 lung cancer, 1 negative diagnosis), and the remaining 9 cases showed negative diagnosis (corresponding histopathology: 5 negative diagnosis, 4 lung

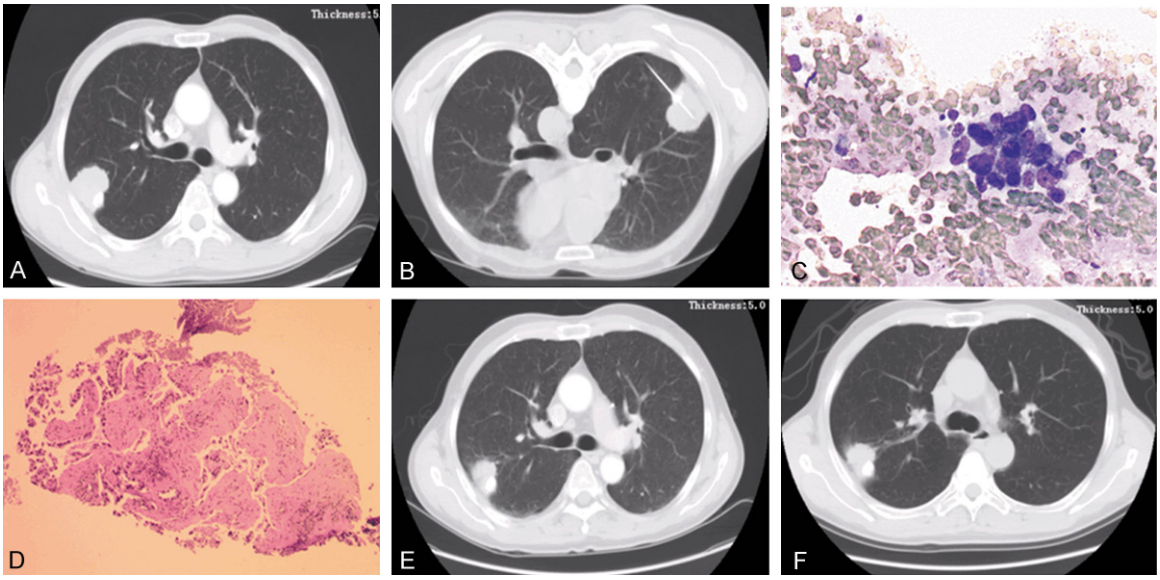

Figure 1. Images from a 61-year-old man with cough. A. Computed tomogram showed a roundish mass in the right lung. B. Axial image with the location of core biopsy needle in the right lung tumor. C. Smear cytology of the biopsy tissue showed cytoplasmic vacuoles, a high nucleus/cytoplasm ratio and coarsely nuclear chromatin in a cluster of cells (× 200), and pathological experts made a definitive diagnosis of lung adenocarcinoma. D. The corresponding histopathology showed no evidence of malignant cells (× 200). E. This patient was diagnosed as lung adenocarcinoma (stage IV) based on the clinical information and smear cytology, then he experienced two cycles gemcitabine plus carboplatin (GC) chemotherapy. The response was evaluated as partial remission. F. Unfortunately, the lesion progressed after four cycles GC.

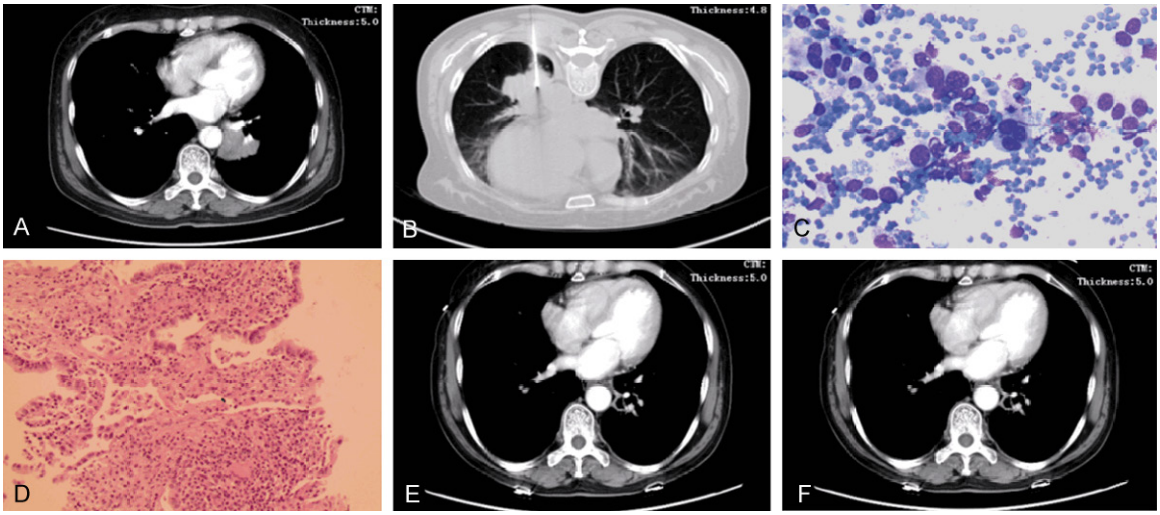

Figure 2. Images from a 63-year-old woman with no symptom. A. Computed tomogram showed an irregular mass in the left lung. B. Axial image with the location of core biopsy needle in the left lung tumor. C. Smear cytology of the biopsy tissue showed similar features with **Figure 1C**, and pathological experts also made a definitive diagnosis of lung adenocarcinoma. D. The corresponding histopathology showed several atypical cells in one or two glands, and pathological experts made an atypical diagnosis. E. The patient was diagnosed as lung adenocarcinoma (stage IIIB) based on the clinical information and smear cytology. She refused to make the gene mutation test, but asked for targeted therapy. After one-month treatment of gefitinib, the lesion disappeared. F. After four-month treatment of gefitinib, the lesion remained disappeared.

cancer) (**Table 3**). For CT guided biopsy (n = 55), smear cytology revealed 32 cases as lung cancer (corresponding histopathology: 29 lung cancer, 2 atypical lesion, 1 negative diagnosis), 7 cases as atypical lesion (corresponding histopathology: 3 atypical lesion, 4 lung cancer), and

the remaining 16 cases as negative diagnosis (corresponding histopathology: 10 negative diagnosis, 1 atypical lesion, 5 lung cancer) (**Table 4**).

Combined the US and CT guided biopsy, the overall consistent rate for smear cytology and histopathology results based on the classification of lung cancer, atypical lesion and negative diagnosis was 69.57% (48/69). The diagnosis rate of lung cancer was 53.62% (37/69) for smear cytology and 66.67% (46/69) for histopathology (P = 0.118). Although 9 (13.04%) more cases were diagnosed as lung cancer by histopathology in this cohort (n = 69), 4 cases (5.80%) were diagnosed as lung cancer by smear cytology (including 1 lung metastasis), not by histopathology (**Figures 1**, **2**).

Comparison of pathological subtypes for lung malignant diseases by smear cytology and histopathology

4 of 37 cases who showed lung cancer by smear cytology failed to further distinguish small cell lung cancer and non small cell lung cancer (corresponding histopathology: 2 adenocarcinoma, 1 squamous-cell cancer, 1 neuroendocrine tumor). Smear cytology revealed 2 cases as small cell lung cancer (corresponding histopathology: 1 atypical lesion, 1 neuroendocrine tumor), 5 cases as non small cell lung cancer (corresponding histopathology: 4 adenocarcinoma and 1 negative diagnosis), 2 cases as squamous-cell cancer (corresponding histopathology: 1 squamous-cell cancer, 1 non-small cell lung cancer), 24 cases as adenocarcinoma (corresponding histopathology: 20 adenocarcinoma, 1 squamous-cell cancer, 1 non small cell lung cancer, 1 poorly differentiated carcinoma, and 1 atypical lesion). 1 case (small cell lung cancer indicated by smear cytology, but atypical lesion by histopathology) that was found a tumor in the left kidney by abdominal CT were diagnosed as renal clear cell carcinoma by renal biopsy.

In patients with malignancy in the smear cytology, it made further pathological classification in the 33 (89.19%) cases, and histopathology shared the same pathological classification rate. The consistent rate of lung cancer subtypes for smear cytology and histopathology was 56.76% (21/37).

Follow-up results

After a median follow-up of 8.45 months (2.12-13.67 months), 10 cases had a definitive diagnosis (1 lung adenocarcinoma by bronchofibroscope, 1 lung squamous-cell carcinoma staged IIIA by surgery, 2 lung cancer by clinical diagnosis due to brain metastasis, 6 lung tuberculosis by further pathological examination or acid-fast bacillus test. The remaining 8 cases still did not have a specific diagnosis. All patients in the follow-up stage were alive except the 2 cases which had brain metastasis.

Discussion

Smear cytology, such as fine needle aspiration cytology (FNAC), is simple, cost effective, readily repeatable, and quick to perform procedure in the outpatient department with excellent patient compliance for thyroid neoplasm [7], cervical lymph node, and breast nodules. Reliable smear cytology mainly depends on the representative specimen from the lesion, the characteristics of the lesion, and correct interpretation for the findings. Because it provides pathological experts only with cytomorphology information, not with information on structure of tumor, and cell number that are essential for a meaningful diagnosis may also be inadequate, its accuracy has been questioned by many clinician all the time. This doubt from clinician is rational. For example, a diagnosis of thyroid follicular carcinoma requires demonstration of vascular or capsular invasion. Therefore, it is impossible to diagnose follicular carcinoma by cytologic examination. Furthermore, the reported accuracy of a specific benign diagnosis made on the basis of transthoracic fine-needle aspiration biopsy ranges from 12% to 57% with median in the 20%-30% range [8]. Despite of all its disadvantages, smear cytology still shows great value in clinical application, especially in the settings of no histopathology. Many literatures indicate that as compared to histopathology, it shows a high accuracy, sensitivity or specificity for the diagnosis of various tumors, such as brain tumors, thyroid lesions, lung cancer [9-11]. In the present study, the method of obtaining smear cytology is different from FNAC that the above series mentioned or bronchoalveolar lavage. We directly smeared the surface of the tumor tissue from the core needle biopsy without extrud-

ing the tissue on a glass slide. This is the first study, to our knowledge, to compare cytology from the core needle biopsy tissue with the corresponding histopathology, aiming to clarify the significance of this additional and simple cytology examination.

In this cohort, the consistent rate of diagnosis for smear cytology and histopathology was about 70%. Though more cases (n = 9) were diagnosed as lung cancer by histopathology than by smear cytology as expected, 4 (5.80%) malignant cases (3 lung cancer, 1 lung metastasis from renal cancer) were diagnosed by smear cytology, not by histopathology. This may be attributed to the damage or loss of malignant cell or tissue from every procedure such as dehydration, fixation, embedding and slicing in histopathology examination. The diagnosis of smear cytology was also supported by plenty clinical evidence in these 4 patients. Thus, it is feasible to enhance accuracy of histopathology by additional smear cytology, although smear cytology is special aspiration cytology. Our result was supported by the study of Yamagami et al that showed the combined use of fine-needle aspiration and core biopsy improves the diagnostic ability of CT-guided lung biopsy [12]. A total of 33 patients were diagnosed as lung cancer by both smear cytology and histopathology, which meant 47.8% patients could get a definitive diagnosis of lung cancer in 10 minutes. Due to many non-malignant cases involved in this cohort, actual percentage would be much higher in patients with lung cancer. This is especially useful for patients to alleviate the anxiety of waiting for the results and for doctors to arrange further examination and treatment as early as possible (such as EGFR gene mutation detection). Furthermore, smear cytology also showed a high classification rate (89.19%) of pathological subtype in malignant cases, which could be compared to that by histopathology. Although histopathology tended to be more accurate in the pathological classification in lung cancer and was the ultimate diagnosis that was used to guide the treatment strategy, these two diagnosis methods made the same pathological subtype in most malignant cases in this cohort. Our results were similar to those of Gupta et al., which indicated FNAC correlated well with histopathology in the diagnosis of solitary thyroid nodule [7].

Typically, a little fluid or bloody material can be attached in the tip of biopsy needle in each procedure. It is similar with the surface substances of biopsy tissue. Since malignant cells can be found in smear cytology of biopsy tissue, it is reasonable to say that malignant cells could also be attached in the surface of biopsy needle, which then can provide clinician with a strong direct evidence for potential implantation metastasis resulted from biopsy, though no implantation metastasis was observed in this study. Furthermore, a high percentage (about 10%) of tuberculosis in this cohort can be due to the select population and rising tuberculosis incidence in some parts of the world [13]. However, only one case got a definitive diagnosis at the initial biopsy, which also indicated that biopsy might have a low sensitivity in the diagnosis of tuberculosis.

Several limitations of our work should be taken into consideration. Firstly, it is a relatively small retrospective cohort. Secondly, the biopsy tissue by CT guidance may be inadequate for those without a specific diagnosis. Lastly, the tumor sizes vary greatly, and this may affect the results of smear cytology and histopathology due to tumor inhomogeneity. In spite of these disadvantages, this special smear cytology indeed shows excellent results.

In conclusion, smear cytology of US or CT guided core needle biopsy tissue is a simple and cost effective diagnosis method, which shows a quick diagnosis and a good correlation with histopathology on lung cancer, and also enhances accuracy of histopathology. Therefore, it is recommended as a routine cytology examination in case of core needle biopsy in lung tumor.

Acknowledgements

We thank all the investigators, including the physicians, nurses, other pathologists, and laboratory technicians in this study.

Disclosures of conflict of interest

None.

Address correspondence to: Yanping Hu and Jing Zhang, Department of Medical Oncology, Hubei Cancer Hospital, 116 Zhuodaoquan South Road,

Hongshan District, Wuhan 430079, Hubei, China. Tel: +86-13971385149; E-mail: hu_yanping1962@126.com (YPH); Tel: +86-18071022046; E-mail: zhangjing9902@126.com (JZ)

References

[1] Sconfienza LM, Mauri G, Grossi F, Truini M, Serafini G, Sardanelli F and Murolo C. Pleural and peripheral lung lesions: comparison of US- and CT-guided biopsy. Radiology 2013; 266: 930-935.

[2] Tsai IC, Tsai WL, Chen MC, Chang GC, Tzeng WS, Chan SW and Chen CC. CT-guided core biopsy of lung lesions: a primer. AJR Am J Roentgenol 2009; 193: 1228-1235.

[3] Rednic N and Orasan O. Subpleural lung tumors ultrasonography. Med Ultrason 2010; 12: 81-87.

[4] Loh SE, Wu DD, Venkatesh SK, Ong CK, Liu E, Seto KY, Gopinathan A and Tan LK. CT-guided thoracic biopsy: evaluating diagnostic yield and complications. Ann Acad Med Singapore 2013; 42: 285-290.

[5] Cao BS, Wu JH, Li XL, Deng J and Liao GQ. Sonographically guided transthoracic biopsy of peripheral lung and mediastinal lesions: role of contrast-enhanced sonography. J Ultrasound Med 2011; 30: 1479-1490.

[6] Yue QF, Xiong B, Chen WX and Liu XY. Comparative study of the efficacy of Wright-Giemsa stain and Liu's stain in the detection of Auer rods in acute promyelocytic leukemia. Acta Histochem 2014; 116: 1113-1116.

[7] Gupta M, Gupta S and Gupta VB. Correlation of fine needle aspiration cytology with histopathology in the diagnosis of solitary thyroid nodule. J Thyroid Res 2010; 2010: 379051.

[8] Liao WY, Chen MZ, Chang YL, Wu HD, Yu CJ, Kuo PH and Yang PC. US-guided transthoracic cutting biopsy for peripheral thoracic lesions less than 3 cm in diameter. Radiology 2000; 217: 685-691.

[9] Malhotra V, Puri H and Bajaj P. Comparison of smear cytology with histopathology of the CT guided stereotactic brain biopsy. Indian J Pathol Microbiol 2007; 50: 862-864.

[10] Sukumaran R, Kattoor J, Pillai KR, Ramadas PT, Nayak N, Somanathan T, George NA and Sebastian P. Fine needle aspiration cytology of thyroid lesions and its correlation with histopathology in a series of 248 patients. Indian J Surg Oncol 2014; 5: 237-241.

[11] Ahmed A and Ahmed S. Comparison of bronchoalveolar lavage cytology and transbronchial biopsy in the diagnosis of carcinoma of lung. J Ayub Med Coll Abbottabad 2004; 16: 29-33.

[12] Yamagami T, Iida S, Kato T, Tanaka O and Nishimura T. Combining fine-needle aspiration and core biopsy under CT fluoroscopy guidance: a better way to treat patients with lung nodules? AJR Am J Roentgenol 2003; 180: 811-815.

[13] Dheda K, Barry CE 3rd and Maartens G. Tuberculosis. Lancet 2016; 387: 1211-26.