

## PAPER DETAILS

TITLE: The Importance of Computed Tomography Guided Transthoracic Aspiration Biopsy/Cell Block Method in Early Diagnosis and Treatment of Lung Lesions: Cytopathologic Analysis in 354 Cases

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# The Importance of Computed Tomography Guided Transthoracic Fine Needle Aspiration Biopsy / Cell Block Method in Early Diagnosis and Treatment of Lung Lesions: Cytopathologic Analysis in 354 Cases

Akciğer Lezyonlarının Erken Tanı ve Tedavisinde Bilgisayarlı Tomografi Eşliğinde Transtorasik İnce İğne Aspirasyon Biopsisi/Hücre Bloğu Yönteminin Önemi: 354 Vakada Sitopatolojik Analiz

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## Abstract

Objective	The aim of this study was to evaluated the effectiveness of computed tomography(CT) guided transthoracic fine needle aspiration biopsy in the diagnosis of lung mass lesions. ( <i>Sakarya Med J</i> 2019, 9(3):513-521 ).
Materials and Methods	In this study, we are presenting 354 CT guided TTFNAB materials. The 348 of aspirations were performed from lung directly and 6 of them were performed from masses with mediastinal location. After the lesion was localized by CT, aspiration biopsy was performed by thoracic surgeon with 20-22 gauge Chiba needle by using 20 ml. If TTFNAB material is sufficient, it was divided into two equal parts for conventional smear cytology and the cell block technique. The results were classified in following categories: 1. Benign/non-neoplastic, 2. suspicious of malignancy, 3. neoplastic-diagnostic, 4. inadequate for interpretation.
Results	Among the 220 patients who underwent TTFNAB (354 aspiration biopsy), 163 (46.04%) were diagnosed as tumor, 74(20.90%) as suspicious lesion, 71 (20.05) as benign lesion and 46 (12.99%) as aspirate nondiagnostic. 140 (39.54%) aspirata cell blocks were applied to 134 cases. Immunohistochemical and histochemical studies were performed in these cases and type differentiation could be made in tumor. Suspicious for neoplasia and neoplastic cases formed major group with 237 cases (66.94%). Among 163 (46.04%) neoplastic aspirates; there were the diagnoses of EC in 58 (35.58%) aspirates, NSC/non-specific in 54 (33,12 %) aspirates, AC in 23 (14.11%) aspirates, SCC in 14 (8.58%), malignant tumor in 8 aspirates, neuroendocrine tumor in 3 aspirates, thymoma in 1 aspirate, plasmacytoma in 1 aspirate and schwannoma in 1 aspirate.
Conclusion	TTFNAB-CB in expert hands and experienced pathologists is fairly accurate for lung masses and can be regarded as an acceptable procedure for early diagnose and treatment planning purposes in most lung lesions.
Keywords	lung; computed tomography; transthoracic fine needle aspiration biopsy; cell block

## Öz

Amaç	Bu çalışmanın amacı, akciğer kitle lezyonlarının tanısında bilgisayarlı tomografi (BT) kılavuzluğunda transtorasik ince iğne aspirasyon biyopsisinin (TTİAB) etkinliğini değerlendirmektir. ( <i>Sakarya Tıp Dergisi</i> 2019, 9(3):513-521 )
Gereç ve Yöntemler	Bu çalışmada 354 BT eşliğinde TTİAB materyalini ve tecrübelerimizi geriye dönük literatür eşliğinde sunmaktayız. Aspirasyonların 348'i direkt akciğer, kalan 6'sı mediasten lokalizasyonlu kitleden yapılmıştı. Lezyonlar BT ile lokalize edildikten sonra göğüs cerrahı tarafından 20ml. 20-22 gauge Chiba iğnesi kullanılarak aspirasyonlar gerçekleştirildi. TTİAB materyalleri yeterli ise konvansiyonel yayma sitolojisi ve hücre bloğu tekniği için iki eşit bölüme ayrıldı. Sonuçlar, aşağıdaki kategorilerde sınıflandırıldı: 1. Benign / neoplastik olmayan, 2. Neoplazi şüpheli, 3. Neoplastik tanısız, 4. Tanımlama için yetersiz.
Bulgular	TTİAB (354 aspirasyon biopsisi) yapılan 220 hastanın 163 (%46.04)'ü tümör, 74 (%20.90)'ü şüpheli lezyon, 71 (%20.05)'i benign lezyon tanısı almış olup, 46 (%12.99) aspirat nondiagnostik özelliktedir. 134 vakadan 140 (%39.54) aspirata hücre bloğu uygulanmış olup bu vakalara immünohistokimyasal ve histokimyasal çalışmalar uygulanabilip tümörlerde tip ayrımı yapılabilmektedir. Neoplazi ve neoplazi şüpheli aspiratlar, 237 (% 66.94) vaka ile ana grubu oluşturdu. Neoplastik 163(46.04%) aspiratın 58'i (35.58%) EC, 54 (33,12 %) aspirat NSC/spesifiye edilemeyen, 23 (14.11%) aspirat AC, 14'ü (8.58%) SCC, 8 aspirat malign tümör, 3 aspirat nöroendokrin tümör, 1 aspirat timoma, 1 aspirat plasmatisom ve 1 aspirat schwannomdu.
Sonuç	Tecrübeli patoloğların uzman ellerinde TTİAB-hücre bloğu incelemesi çoğu akciğer lezyonunun erken tanı ve tedavi planlaması için uygun bir yöntem olarak kabul edilebilir. Pnömotoraks gibi basit ve tedavi edilebilir komplikasyonları olduğundan popülerliği klinisyenler, radyologlar ve patoloğlar arasında artmaktadır
Anahtar Kelimeler	akciğer; bilgisayarlı tomografi; transtorasik ince iğne biopsisi; hücre bloğu

## INTRODUCTION

Lung cancer remains one of the leading causes of cancer mortality world wide. Much of the cases are at the advanced stage on diagnosis.<sup>1</sup> Early diagnosis have been shown to increase survival in localized lung cancer. Transthoracic fine needle biopsy was used for the first time by Leyden in order to take bacteriological samples at the end of the 19th century, by Menetrier soon afterwards for the diagnosis of lung cancer.

Computed tomography (CT) guided transthoracic fine needle aspiration biopsy (TTFNAB) is a commonly used diagnostic method with the help of developing radiological methods in lung disease especially lung cancer.<sup>2</sup> All intra-thoracic lesions are now routinely and safely using TTFNAB under CT.<sup>3-6</sup> It is a rapid diagnostic method which can be selected firstly in particular for the lesions smaller than a few centimeters localized at mediastinum, pulmonary apex, medial upper lobe or periphery. However, the use of this method often results in pneumothorax development.<sup>4</sup> Recognition of the accuracy of TTFNAB and simpler methods of treating pneumothorax has brought this method within the reach of most hospital radiologists and pathologists.<sup>7-12</sup>

It is known as a reliable method with limited morbidity risk and simple procedure with good patient acceptance.<sup>7</sup> The value of the diagnosis decreases in cases of inadequate sampling and taking necrotic material.

The diagnosis rate and accuracy in the making of differentiation of small cell carcinoma (SCC) and nonsmall cell carcinoma (NSCC) in tumor typing increased more with the cell block method applied to aspirates in recent years with the implementation of histochemical and immunohistochemical staining.

As the majority of lung cancer is the diagnosed on aspiration cytology, or small biopsy samples, often obtained by increasingly experienced diagnostic procedures, the pa-

thologist must obtain maximal diagnostic yield from cytology specimens. In about 90 percent of patients, needle biopsy provides enough tissue for the pathologist to determine the cause of the abnormality.<sup>13,14</sup>

While differentiation of SCC and NSCC is certainly important for radical surgical procedure, now subtyping should be done in NSCC. Because, the specific subtypes have different answers from each other to various chemotherapeutic agents.<sup>14</sup>

The purpose of this retrospective study, determination of early diagnosis value, reliability, success of type determination in tumors and various lung lesions of CT guided TTFNAB and cell blocks was intended.

## Materials and Methods

In this study, we are presenting 354 CT guided TTFNAB materials and our experience with literature. Results were evaluated retrospectively. The 348 of aspirations were performed from lung directly and 6 of them were performed from masses with mediastinal location. The lesion was localized by CT aspiration biopsy was performed by thoracic surgeon with 20-22 gauge Chiba needle by using 20 ml. injector. The patient was watched carefully for signs of pneumothorax and a follow-up X-ray performed four hours after the TTFNAB to look for any such signs. Fresh TTFNAB was received. If the material is sufficient, it was divided into two equal parts. One part was subjected to conventional smear cytology (CS) and the other part for the cell block (CB) technique.

In conventional smear technique; the sent material was centrifuged at 2500 rpm for 10-15 minutes. A minimum of two thin smear slides were prepared from the precipitate. One slide was prepared after air drying and stained with the May-Grünwald-Giemsa stain (MGG). The other slide was urgently fixed in 95% alcohol and stained with the Papanicolaou stain (Pab). In CB technique; the adequate material that remained was subjected to fixation for one

hour by mixing with alcohol-formalin. After fixation, this fluid material was centrifuged at 2500 rpm for 10-15 minute. Tube taken from the bottom sediments of blotting paper soaked in alcohol. On the following day, this cell button sediment sample was processed along with routine histopathological specimens. CB sections of 5–6 µ thickness were prepared and stained with the hematoxylin and eosin stain (HE). Special stains like the periodic acid Schiff (PAS), mucin, pas-alcian blue and immunohistochemical stain were performed wherever necessary. Classification of lung tumors was made according to the 2004 World Health Organization (WHO). The results were classified in following categories: 1. Benign/non-neoplastic, 2. suspicious of malignancy, 3. neoplastic-diagnostic, 4. inadequate for interpretation (Table I).

Table I- Cytological diagnosis of pulmonary mass lesions		
Cytological categories	Number of cases (n:354)	Percentage (%)
Non-neoplastic	71	20.06
Suspicious malignancy	74	20.90
Neoplastic-diagnostic	163	46.05
Inadequate	46	12.99

Necrotic materials were also included into the suspicious aspirates. Neoplastic materials were divided into NSCC / non-specific, epidermoid carcinoma (EC), adenocarcinoma (AC), small cell carcinoma (SCC) and other tumors. Cell block was prepared for 140 TTFNAB. Histopathologic examinations of the 71 cases could be done, cytologic diagnoses were compared with tissue diagnoses (Table II).

This study is a descriptive research.

The study was approved by the Ethical Committee of the institution.

There are no conflict interest.

TABLEII- The histopathological results		
Cytologic diagnosis	Histopathologic diagnosis	Number of cases (n:354)
Non-diagnostic/inadequate	Nonspecific inflammation	4
	Cyst hydatid	2
	Timic cyst	1
	Hodgkin Lymphoma	1
	Bronchial Tissue	1
Suspicious for malignancy	Squamous cell carcinoma	1
	High grade dysplasia	1
	Nonspecific inflammation	3
	Malign mesothelioma	2
	PNET	1
	Atypical Carcinoid	1
	Malign tumor	1
	Small cell carcinoma	2
	NSCC	3
	Epidermoid carcinoma	6
Benign conditions	Nonspecific inflammation	5
	Aspergillosis	1
	Thymoma	1
	Adenocarcinoma	1
	Malign lymphoma	1
	Epidermoid carcinoma	2
	Undifferentiated carcinoma	1
	Small Cell Carcinoma	1
	Necrotic tissues	1
	Small Cell Carcinoma	1
	Epidermoid Carcinoma	1
	Moderate dysplasia	1
	Transitional cell carcinoma	1
	Epidermoid carcinoma	7
	Adenocarcinoma	1
	Small round-cell malignancies	1
	Adenocarcinoma	2
	Inflammatory events	1
NSCC / unclassified	Adenocarcinoma	4
	NSCC	3
	Inflammatory events	3
	Plasmacytoma	1
	Schwannoma	1
Thymoma	Thymoma	1
NSCC: non small cell carcinoma PNET: primitive neuroectodermal tumor		

## RESULTS

Total number of 220 patients-354 TTFNABs were selected for the study. The age ranged was from 31 to 89 years, with an average of 63.78 years. One hundred forty CBs from 354 aspirates brought to our laboratory were prepared for 134 patients. Only 11 of the CB (7.85%) were non-diagnostic, the failure rate was decreased more by applying the CB. One hundred twenty five CB preparations with adequate cellularity were subjected to histochemical and / or immunohistochemical staining. Forty-six (12.99%) of the 354 TTFNAB materials examined were non-diagnostic aspirates, the remaining 308 (87.00%) aspirates were adequate and could be diagnosed. The distribution of the 354 aspirated diagnosed with needle aspiration and CB.

Seven cyst hydatid, 1 aspergillus fungal infection, 1 granulomatous reaction were available in 71 (20,05%) aspirates with benign diagnosis, the remaining benign lesions were constituted with abscesses and inflammatory events(Table III).

Table III- Sub-categorization of cytologically non-neoplastic lesions	
Non-neoplastic lesion(n:71)	Number of cases
Cyst hydatid	7
Aspergillus	1
Granulomatous inflammation	1
Abscess	10
Chronic non-specific inflammation	52

Fourteen (18.91%) of 74 (20.90%) suspicious aspirates were necrotic material. As expected, suspicious for neoplasia and neoplastic cases formed major group with 237 cases (66.94%). Among 163 (46.04%) neoplastic aspirates; there were the diagnoses of EC in 58 (35.58%) aspirates (Figure 1,2), NSCC/non-specific in 54 (33,12 %) aspirates, AC in 23 (14.11%) aspirates(Figure 3), SCC in 14 (8.58%), malignant tumor in 8 aspirates, neuroendocrine tumor in 3 aspirates, thymoma in 1 aspirate, plasmacytoma in 1 aspirate and schwannoma in 1 aspirate (Table IV).

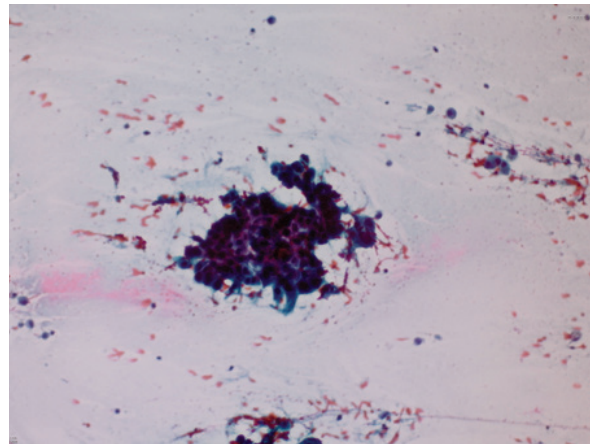


Figure I. Epidermoid carcinoma, neoplastic cells with keratinized cytoplasm MGGx100

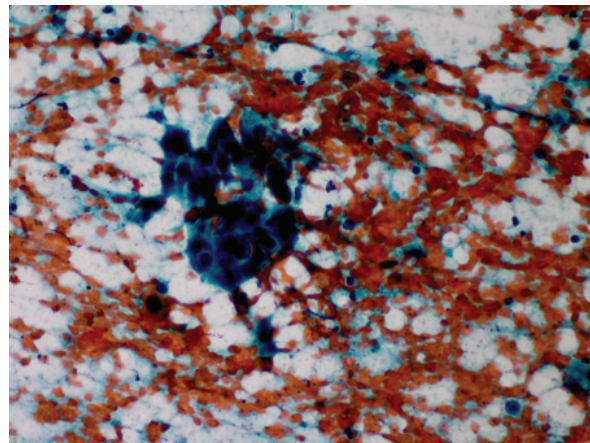


Figure II. A cluster of neoplastic squamous cells with pleomorphic cells having eosinophilic cytoplasm Papx200

Table IV-Types of neoplasia diagnosed in TTFNAB		
Type of neoplasia	Number of cases(n:163)	Percentage(%)
Epidermoid carcinoma	58	35.58
NSCC/non-specific	54	33.13
Adenocarcinoma	23	14.12
Small cell carcinoma	14	8.59
Malign tumor	8	4.90
Neuroendocrin tumor	3	1.85
Tymoma	1	0.61
Plasmacytoma	1	0.61
Schwannoma	1	0.61
NSCC:non small cell carcinoma TTFNAB:transthoracic fine needle aspiration biopsy		

Tissue diagnoses of 71 aspirates were available histopathologically. The tissue diagnoses of 10 inadequate aspirates were: inflammatory events in 4 of them, hydatid cysts in 2 of them and the rest were thymic cysts, Hodgkin's lymphoma, EC, nonspecific bronchial biopsy. Tissue diagnoses of 20 suspicious aspirates were available; inflammatory event in 3 of them, EC in 6 of them, SCC in 2 of them, malignant tumor in 1 of them, atypical carcinoid in 1 of them, PNET in 1 of them, malignant mesothelioma in 2 of them, inflammatory event in 1 of them. Tissue diagnoses of 30 neoplastic aspirates were available; tumor was not observed in 6 of them, 4, 1 and 1 of them were reported to be inflammatory event, tumor necrosis and moderate dysplasia, respectively and they were reflecting the neighboring area of the tumor.

### DISCUSSION

It has been reported since 1883 in publications on this subject in the literature that TTFNAB was a safe method with high diagnostic value in benign and malignant masses and infectious diseases of lung.<sup>15-20</sup>

Different imaging modalities such as ultrasonography, fluoroscopy, and computed tomography have been used by various authors.. Computed tomography is widely used.<sup>7,12,15,24</sup> In our study we have used CT which is the most commonly used method today.

The most important indications are lung nodules and masses, mediastinal and hilar lesions, metastatic lesions, chest wall invasion and consolidation and infiltration which may also be caused by infection. The diagnosis rates has been reported above 80% for malignant lesions in various studies.<sup>3</sup> This rate decreases to 12-68% in benign lesions.<sup>4,5</sup> The main cause of becoming a common diagnostic procedure of this method is that the lesion can be reached easily with especially with accompaniment of CT, which was began to be widely used especially in recent years, and the material is taken directly from the lesion with minimum artefacts and more cellular and adequate

sample is provided, unlike other pathological and cytological methods.<sup>7</sup>

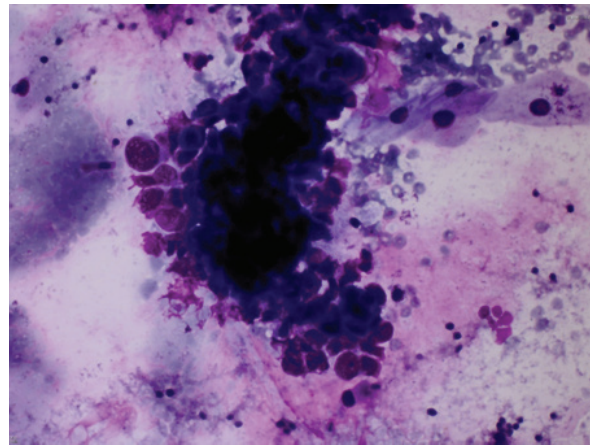


Figure III. Adenocarcinoma, neoplastic cells with delicate cytoplasm and pleomorphic nucleus-prominent nucleoli MGGX400

Inadequate sampling rate in TTFNAB in the literature varies between 8.8% and 25.4%<sup>23,25</sup>. In our study this rate was 12.99% (46/354), this shows that entering into the mass accurately accompanied by CT is important which is compatible with the literature. It draws attention that this rate in our study decreased to 7.88% (11/354) with the cell block application and had higher adequacy.

CB method increased high cellularity (Figure 4), more obvious morphological features, accuracy of cytological diagnosis in the identification of malignant cells and the rate of early diagnosis.<sup>26</sup> In 1928, Zemansky concluded that the CB method was superior to the CS technique and that examination of materials other than pleural and ascitic fluids was unreliable.<sup>27</sup>

In addition, performing cell block on the materials taken provides significant advantages. Re-evaluation with serial sections when hematoxylin and eosin staining, which is a routine method, was required in patients with tumor suspicion and performing auxiliary pathological additional methods such as histochemical-immunohistochemical



staining when necessary. It is possible to make a diagnosis equivalent to histopathological examination and subtyping of tumors with this method.

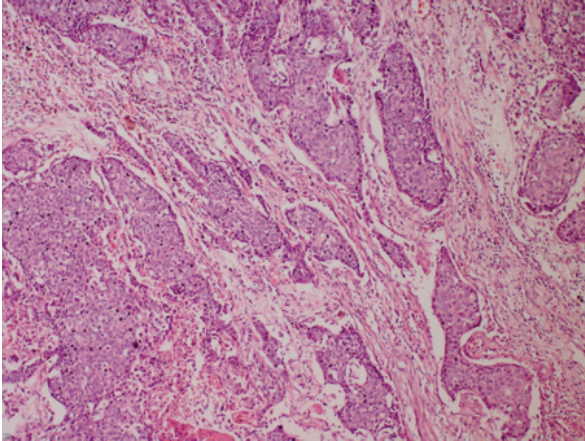


Figure IV. Cell block with high cellularity HEx200

More reliable diagnosis can be made earlier in the sections with less cellularity with cell block method. In this study, 140 CB have been prepared in 354 aspirates for 134 patients. Only 11 of the CBs (7.8%) were non-diagnostic, the failure rate has been reduced even further with the application of CB. The histochemical and / or immunohistochemical staining were applied to 125 CB preparations with adequate cellularity. While cytokeratin7 (CK7), cytokeratin 5-6, p63 were present in our panel for EC (Figure 5,6), one or more antibodies were selected such as TTF1, CK7, mucin, pas-alcian blue histochemistry for AC and CK7, CD45, CD56, synaptophysin and chromogranin for SCC (Figure 7,8). While making the discrimination of SCC and NSCC in lung tumors has importance for surgery, today pathologists should give the specific types of NSCC as much as possible to oncologists and radiation oncologists. Because, specific subtypes of NSCC display varying responses to different chemotherapeutic agents. Tumor classification and accurate staging to allow treatment planning and the identification of patients who will benefit from potentially curative redical treatment). In our study, 58 (42.96%) and 23 (17.03%) of 135 NSCC were reported to be EC and AC respectively.

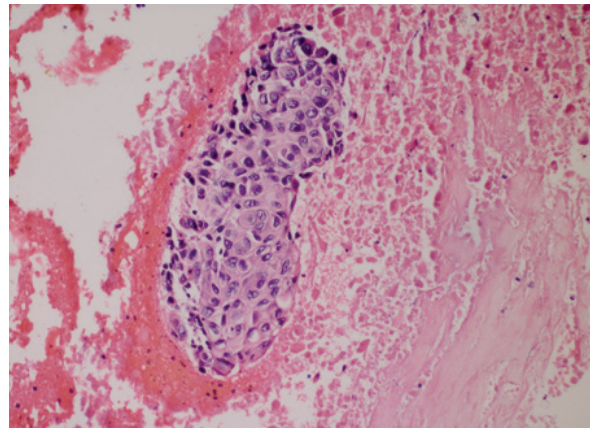


Figure V. Epidermoid carcinoma, cell block HEx200

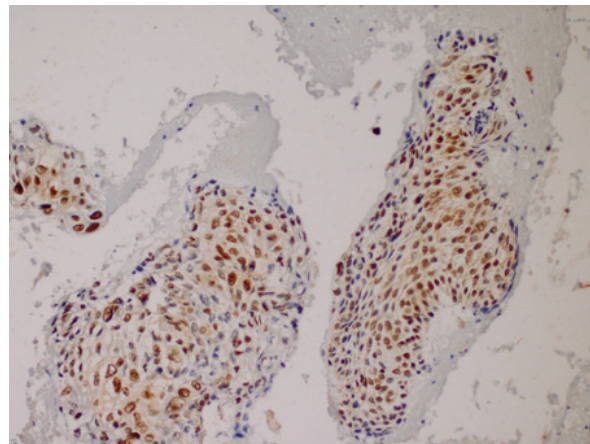


Figure VI. Epidermoid carcinoma, p63 immunohistochemicalstainingx400

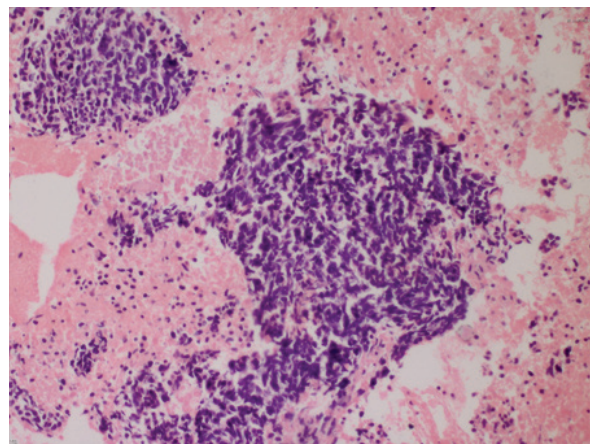


Figure VII. Neoplastic small cell with scant cytoplasm and crush artefact HEx400

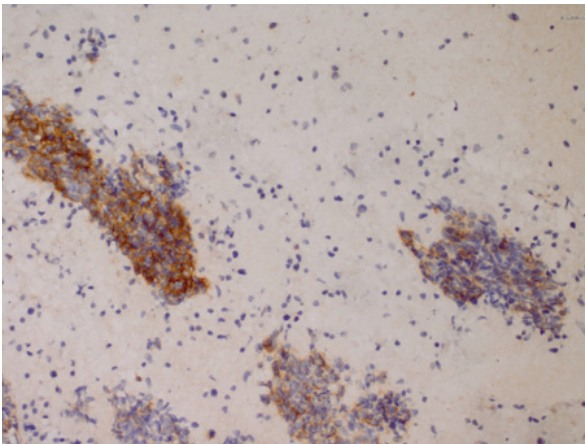


Figure VIII. Small cell carcinoma, CD56 immunohistochemical stainingx200

The sub-typing could not be performed in 54 cases and they were diagnosed as NSCC. Literature reveals that 70% of the primary lung cancers are diagnosed as NSCC, whereas SCC are found to comprise around 20% of all primary lung tumors. In our study, 135 (90.6%) and 14 (9.3%) of 149 primary lung cancer were reported to be NSCC and SCC, respectively. We thought that the difference with the literature was caused due to SCC cases which involve extensive areas of necrosis were considered among the suspicious lesions as necrotic material. The diagnostic value of TTFNAB, which is quite diagnostic for malignant lesions, is lower for benign lesions. In benign lesions; the diagnosis rates of TTFNAB is reported to be 12-68%.<sup>4</sup> In our study, 6 (50%) of the 12 cases with tissue diagnosis and diagnosed as benign with TTFNAB were diagnosed as benign. The other six cases, although cytology was reported as benign, were diagnosed as malign histopathologically. Two of these cases were malignant lymphoma that lymphoid cells on the ground were interpreted as inflammatory events. One of them was thymoma that lymphoid cells were on the ground and epithelial area. was not found in the smear. The tissue diagnosis of other 4 cases were 2 EC, 1 AC, 1 undifferentiated carcinoma. When the smears and CBs were re-evaluated, it has been seen that the smears reflected the changes of tumor-adjacent areas and the actual mass was

not fully entered. The evaluation was difficult for 2 cases due to smear and staining artifacts in the preparations caused by technical reasons.

Santambrogio et al.<sup>10</sup> have reported the sensitivity, specificity and efficiency for malignant lesions as 98.5%, 100% and 99.1%, respectively in their series with 110 cases; Moulton et al.<sup>11</sup> have reported as 84%. In our study, the tissue diagnoses in 24( 70.58%) of 34 cases with tumor diagnosed in 54 TTFNAB with histopathological tissue diagnosis were also reported as tumor.

It was thought that the cases, which were not diagnosed histopathologically, were caused by the problems of biopsy material such as difficulties in taking of tissue from the correct place and adequately, tissue loss and disorders in laboratory procedures. When it was considered that the biopsy diagnosis were necrotic tissue, dysplastic changes and inflammatory reactions, it was seen that the biopsies were taken from adjacent areas of the tumor. Therefore, if clinico-radiological correlation is present in cases diagnosed positively with TTFNAB-CB, we believe that histopathological diagnosis is not required with repeated biopsy.

The discrimination of SCC and NSCC could be performed in 149 cases of 169 smear diagnosed with tumor, 14 of them were SCC and 135 of them were NSCC. Fifty-eight and 23 of the 81 NSCC cases were EC and AC respectively. TTFNAB-CB in expert hands and experienced pathologists is fairly accurate for typing lesions and can be regarded as an acceptable procedure for diagnostic and medical treatment with chemotherapeutic agents planning purposes in most NSCC cases. In poorly differentiated and suspicious cases, the use of ancillary techniques, such as immunohistochemical or histochemical stains, may be required to improve the diagnostic yield.

In conclusion; when CT guided TTFNAB is applied in the early diagnosis of intrathoracic mass lesions and CB slights can be prepared and auxiliary techniques can be



used, it is a cheap, effective, reliable method which has a high diagnostic value and a reasonable complication rate. Its popularity is increasing among clinicians, radiologists and pathologists due to it is a simple method and has a complications such as pneumothorax, which can be treated. TTFNAB should be used at an early stage and more often in order to shorten the diagnosis time of lung cancer and to ensure a faster treatment.

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