ORIGINAL ARTICLE
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UDC: 616.24-006-07
DOI: https://doi.org/10.2298/VSP200618117D

Correlation between cytological and histopathological diagnosis of non-small cell lung cancer and accuracy of cytology in the diagnosis of lung cancer

Korelacija citološke i histopatološke dijagnoze nemikrocelularnog karcinoma pluća i tačnost citologije u dijagnostici karcinoma pluća

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Abstract

Background/Aim. Lung cancer is one of the most common cancer types worldwide. More than 70% of patients are diagnosed with lung cancer in the advanced stages of the disease, with limited therapeutic options based on cytological and histopathological material. The value of cytology in diagnosing and subtyping non-small cell lung cancer (NSCLC) is very important for modern personalized therapies. The aim of this study was to find out the concordance between cytological and histopathological diagnosis of NSCLC and the accuracy, sensitivity, specificity, and the positive and negative predictive value of cytology in diagnosing lung cancer. **Methods.** A two-year retrospective study included 169 patients with cytological diagnosis of NSCLC, who, at the same time, had small biopsy and surgical specimens for histopathological diagnoses confirmation that were compared with cytological one. Histopathological diagnosis on surgical specimens was the golden standard for evaluation concordance to the cytological diagnosis of NSCLC and evaluation accuracy, specificity, sensitivity, and the positive and negative prognostic value of cytology as a diagnostic method for detecting lung cancer. **Results.** This study included 129 (76.3%) male and 40 (23.7%) female patients, aged between 39 and 83, with the average of 62.53 ± 7.6. There was no statistically significant difference between the ages of different genders ($p = 0.207$). The most frequent diagnosis among cytological diagnoses was NSCLC in 99 (58.58%) patients. Concordance between cytological and histopathological diagnoses of surgical specimens was 61.48%. There was no statistically significant difference between cytological diagnoses and histopathological diagnoses of small biopsies specimens ($p = 0.856$). The sensitivity, specificity, positive and negative prognostic value, and accuracy of cytology as a diagnostic method of lung cancer were 94.98%, 98.60%, 95.72%, 98.35%, and 97.71%, respectively. **Conclusion.** Cytological diagnosis of NSCLC is accurate, with high sensitivity, specificity, and benefits for patients. Most patients are diagnosed with advanced cancer when there is no surgical therapy option, and the only available diagnostic material is a small biopsy sampled during bronchoscopy.

Key words:
biopsy; bronchoscopy; carcinoma, non-small-cell lung; cytological techniques; histological techniques; prognosis; sensitivity and specificity.

Apstrakt

Uvod/Cilj. Karcinom pluća je jedan od najučestalijih karcinoma u svetu. Kod više od 70% bolesnika dijagnostikuje se u odmaklim stadijumima bolesti kada su terapijske mogućnosti ograničene i zasnovane na dijagnozi citološkog ili patohistološkog materijala. Kod novih personalizovanih vidova terapije veliki je značaj citologije u dijagnostici i subtipizaciji nemikrocelularnih karcinoma pluća (*non-small cell lung cancer* – NSCLC). Cilj rada bio je da se utvrdi podudarnost između citološke dijagnoze NSCLC i patohistološke dijagnoze, kao i tačnost, senzitivnost, specifičnost, i pozitivni i negativni prognostički značaj citologije u dijagnostici karcinoma pluća. **Metode.** Istraživanje je sprovedeno kao retrospektivno i obuhvatilo je 169 bolesnika kojima je tokom dve godine dijagnostikovan NSCLC na citološkom uzorku, pri čemu su bolesnici istovremeno imali i uzorak male biopsije, kao i hirurški uzorak za patohistološku dijagnostiku, čije dijagnoze su upoređivane sa citološkom dijagnozom.

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Patohistološka dijagnoza na hirurškim uzorcima bila je zlatni standard za utvrđivanje podudarnosti između citološke dijagnoze NSCLC i patohistološke dijagnoze, kao i tačnosti, senzitivnosti, specifičnosti, pozitivnog i negativnog prognostičkog značaja citologije kao metode u dijagnostici karcinoma pluća. **Rezultati.** U istraživanje je bilo uključeno 129 (76,3%) muškaraca i 40 (23,7%) žena, starosti između 39 i 83 godina, prosečno 62,53 ± 7,6. Nije bilo statistički značajne razlike u starosti bolesnika različitog pola ($p = 0,207$). Među citološkim dijagnozama najčešći je bio NSCLC kod 99 (58,58%) bolesnika. Podudarnost između citoloških i patohistoloških dijagnoza bila je prisutna kod 61,48% bolesnika. Nije bilo statistički značajne razlike između citoloških i patohistoloških dijagnoza materijala male biopsije ($p = 0,856$). Citologija, kao dijagnostička metoda za karcinom pluća pokazala je senzitivnost 94,98%, specifičnost 98,60%, pozitivni prognostički značaj 95,72%, negativni prognostički značaj 98,35% i tačnost 97,71%. **Zaključak.** Citološka dijagnostika NSCLC je tačna, visoko senzitivna i specifična i korisna za bolesnike. Kod većine bolesnika dijagnoza se postavlja u odmaklom stadijumu bolesti, kada je karcinom inoperabilan, a jedini dostupni materijal za postavljanje dijagnoze je mala količina materijala dobijeng tokom bronhoskopije.

Ključne reči:
biopsija; bronhoskopija; pluća, nesitnoćelijski karcinom; citološke tehnike; histološke tehnike; prognoza; senzitivnost i specifičnost.

Introduction

In the last seven decades, lung cancer has been the most common cancer worldwide, with 1.8 million new cases per year. It is the most common cause of cancer death worldwide [1]. More than 70% of patients were diagnosed in advanced stages of diseases; therefore, diagnostic possibilities are often limited to cytological diagnosis and/or histopathological diagnosis on small biopsies. For a few years, it was sufficient to distinguish between small cell lung cancer and non-small cell lung cancer (NSCLC) without further subtyping [2]. According to the last recommendations of the International Association for the Study of Lung Cancer, the American Thoracic Society, the European Respiratory Society, and the World Health Organization (WHO), novel therapeutic methods need subtyping of NSCLC even on cytological samples and small biopsies, whenever possible [3–5].

Based on WHO recommendations for diagnosing by examining cytological samples and small biopsies, lung adenocarcinoma is an epithelial malignant tumor morphologically with glandular differentiation, vacuolated cytoplasm, mucin production, enlarged nuclei, or specific immunohistochemical marker expression – napsin-A or thyroid transcription factor-1 (TTF-1) positivity after immunostaining. Squamous cell lung cancer is an epithelial malignant tumor morphologically with keratinization, dense cytoplasm, intracellular bridges, or specific immunohistochemical marker expression – p40 or p63 positivity after immunostaining. NSCLC, not otherwise specified (NOS), includes cancers without either morphological characteristics specific for adenocarcinoma or squamous cell carcinoma or immunostaining positivity [4, 6].

Accuracy, sensitivity, specificity, and positive and negative prognostic value of cytology in diagnosis and staging of NSCLC have been monitored since 1980. Plenty of cytological methods of sampling are in use, including exfoliative methods (sputum, bronchoalveolar lavage – BAL, bronchial aspiration, and brush cytology) and aspiration methods (transbronchial needle aspiration – TBNA) [7]. Nowadays specificity of cytology is up to 100% and sensitivity between 60% and 90%, depending on the sampling method. Ultrasound-guided TBNA has increased the sensitivity of cytology and decreased the number of false negative cytological diagnoses. The value of cytology in diagnosing NSCLC and subtyping it to adenocarcinoma and squamous cell carcinoma is very important for modern personalized molecular therapies and immunotherapy, while rapid diagnostic on small samples is preferred for patients' benefit, fewer complications while sampling, and appropriate therapy time [8].

The aim of this study was to find out the concordance between cytological diagnosis of NSCLC and histopathological diagnosis and the accuracy, sensitivity, specificity, and positive and negative predictive value of cytology in diagnosing lung cancer.

Methods

A two-year retrospective study was conducted at the Department of Cytology of the Institute of Pathology and Forensic Medicine of the Military Medical Academy (MMA) in Belgrade, Serbia. All the patients in this study first went on bronchoscopy because of clinical or radiological suspicion of lung cancer. Material for cytological and histopathological evaluation was taken during bronchoscopy. In those two years, the total number of patients with the suspicion of lung malignancy that was first diagnosed on cytological and small biopsy material, following histopathological confirmation on surgical material, was 1,047. Among those patients, 251 (23.97%) were cytologically malignant, and 169 (67.33%) had an NSCLC diagnosis. Those 169 patients with NSCLC cytological diagnosis were included in this study.

Criteria for inclusion of patients in the study were bronchoscopically or radiologically visible tumorous formation in the lungs and cytological, histopathological diagnosis on small biopsy and surgical material for each patient. Patients with previous chemotherapies, radiotherapies and malignancies were excluded from this study.

Demographical data (gender and age) and diagnostic procedure details were collected from patients' information databases of the MMA, Institute of Pathology, and Department of Cytology.

The material was sampled for cytological and histopathological analysis during video-assisted bronchoscopy (Olympus BF260 and Karl Storz, GmbH&Co.KG. Tuttlingen, Germany) of an analgosedated patient. Cytological methods of sampling included: TBNA using needle 19G (for tumors not visualized in bronchial lumen), brush cytology, bronchial content aspiration, sputum or BAL (for centrally located tumors in bronchial lumen), and "tru-cut" needle biopsy (for tumors localized on the periphery of the lung).

Among patients, 78.60% had material sampled using only one method, 20.20% of patients had material sampled using two, and 1.20% using three methods. Cytological methods of sampling are presented in Figure 1.

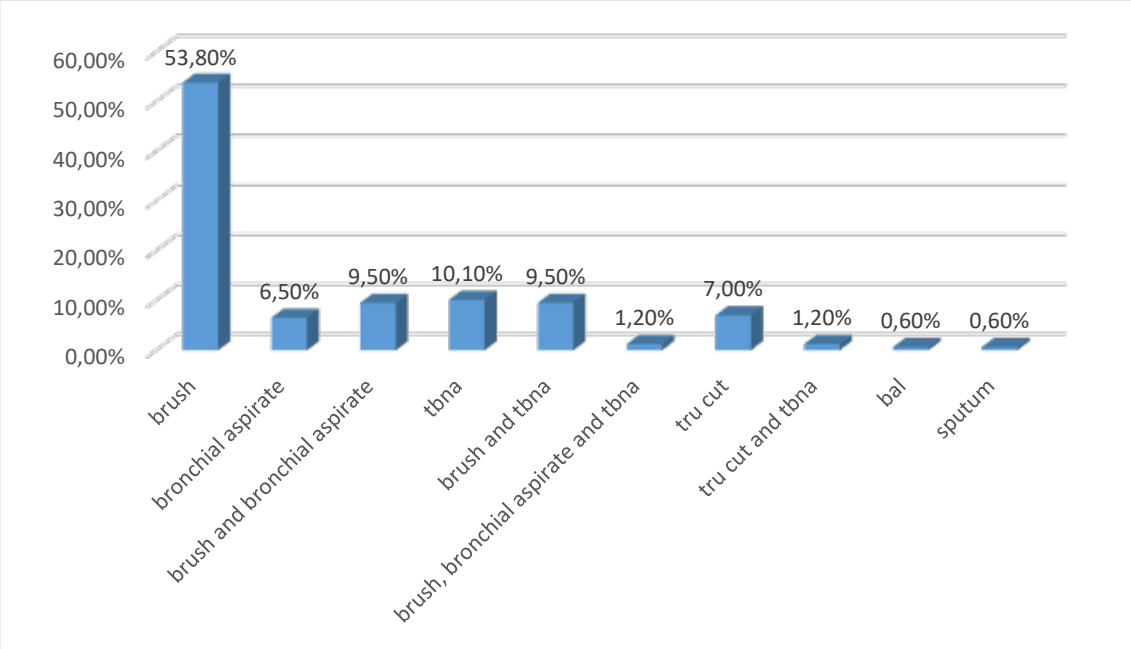


Fig. 1 – Cytological methods of sampling.
tbna – transbronchial needle aspiration; bal – bronchoalveolar lavage.

Cytological smears were made on microscopic slides from the material of each patient; moreover, cytospins were made in cases of large amounts of material. Microscopic slides were air-dyed and stained by May-Gruenwald-Giemsa (MGG) method. After microscopic evaluation, cytological diagnoses that were made were malignant – NSCLC, adenocarcinoma, or squamous cell carcinoma.

Material for small biopsy histopathological evaluation was sampled simultaneously with cytological material during bronchoscopy using bronchial biopsy or TBNA with a 19 G needle. It was fixed in buffered 4% formalin for 12 h, dehydrated by increased alcohol concentration, cleared by chloroform, embedded in paraffin, and cut by microtome (Leica) to slices measured 4 μm. After that, it was deparaffinized and stained by hematoxylin and eosin. Immunostaining methods were used in small biopsies samples in poorly differentiated tumors (CK7 and TTF-1 for confirmation of lung adenocarcinoma and p63 for confirmation of squamous cell lung cancer). Both cytological and histological slides were analyzed using a microscope (Olympus BX50) with a digital camera Olympus SC50 and computer software CellSense. Criteria for diagnoses on cytological and small biopsies material were according to the newest WHO 2015 recommendations [4].

Histopathological diagnosis on surgical specimens was the golden standard for the evaluation of specificity and sensitivity of cytology as a diagnostic method for detecting lung cancer. True positive is a malignant cytological sample confirmed after histopathological analysis as malignant. True negative is a benign cytological sample confirmed after histopathological analysis as benign. False positive is a malignant cytological sample and benign histopathological diagnosis. False negative is a benign cytological sample and malignant histopathological diagnosis.

Sensitivity measured a proportion of true positive cytological samples and the sum of true positive and false negative cytological samples. Specificity measured a proportion of true negative cytological samples and the sum of true negative and false positive cytological samples. The positive prognostic value measured a proportion of true positive cytological samples and the sum of true positive cytological and false positive samples. The negative prognostic value measured true negative cytological samples and the sum of true negative cytological and false negative samples. Accuracy measured a proportion of the sum of true positive and true negative cytological samples and the number of all samples [9].

All the data were statistically analyzed using the software package IBM SPSS 24. Statistical analysis included methods of descriptive statistics (mean value ± standard deviation and relative numbers), parametrical Student's *t*-test and ANOVA for numerical variables, non-parametrical Mc Nemmar and Kruskal-Wallis test for nominal variables, and

non-parametric Kendal-Tau correlation coefficient. The level of statistical significance was considered to be $p < 0.05$.

Results

A two-year retrospective study was done on 169 patients, including 129 (76.3%) male and 40 (23.7%) female patients. There was a statistically significant difference between the number of male and female patients, $p < 0.0001$.

Patients were aged 39 to 83 years, with an average of 62.53 ± 7.6. The age of the male patients was between 46 and 83 years, with an average of 63.29 ± 7.29. The age of the female patients was between 39 and 79 years, with an average of 60.1 ± 8.13. There was no statistically significant difference between the ages of different genders, $p = 0.207$.

The most frequent cytological diagnosis was NSCLC in 99 (58.58%) patients. Squamous cell carcinoma was diagnosed in 45 (26.63%) patients and adenocarcinoma in 22 (13.02%) patients. Only 3 (1.77%) patients had atypical cells suspicious of NSCLC in cytological samples.

The most common histopathological diagnosis, according to small biopsies samples, was squamous cell carcinoma in 79 (46.75%) patients. Adenocarcinoma and NSCLC, NOS were found in 77 (45.56%) and 10 (5.92%) patients, respectively. Non-Hodgkin lymphoma was diagnosed in 2 (1.18%) patients and plasmacytoma and metastasis of prostate adenocarcinoma each in 1 (0.59%) patient.

Squamous cell carcinoma, found in 78 (46.15%) patients, was the most frequent diagnosis in surgical histopathological specimens. Adenocarcinoma was found in 77 (45.56%) patients following NSCLC, NOS in 2 (45.56%), large cell lung carcinoma in 2 (1.18%), and Non-Hodgkin lymphoma 2 (1.18%) in patients (Figure 2). Large cell neuroendocrine carcinoma, plasmacytoma (Figure 3), epithelioid mesothelioma, carcinosarcoma, mucoepidermoid carcinoma, germ cell tumor, and prostate adenocarcinoma (Figure 4) were found each in 1 (0.59%) patient.

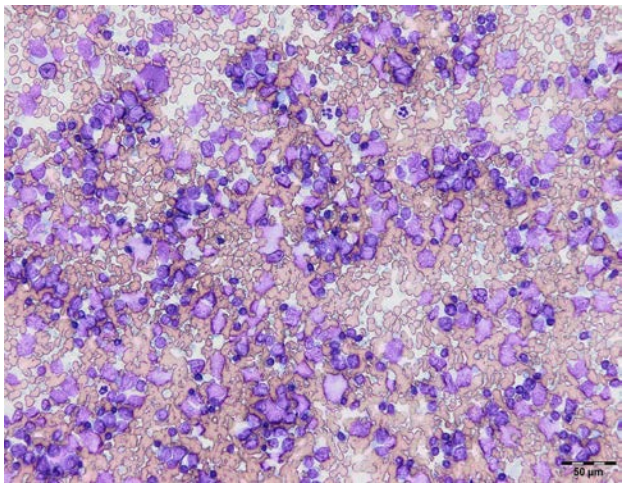


Fig. 2 – Cytologicially diagnosed non-small cell lung cancer with histopathological Non-Hodgkin lymphoma diagnosis (May Grunwald-Giemsa stain, ×200).

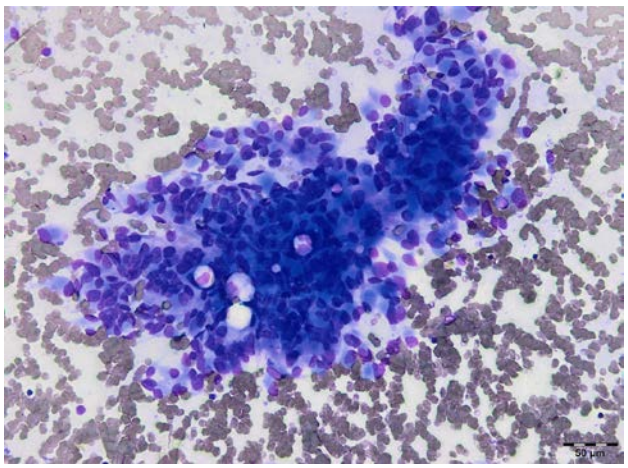


Fig. 3 – Cytologically diagnosed non-small cell lung cancer with histopathological plasmacytoma diagnosis (May Grunwald-Giemsa stain, ×200).

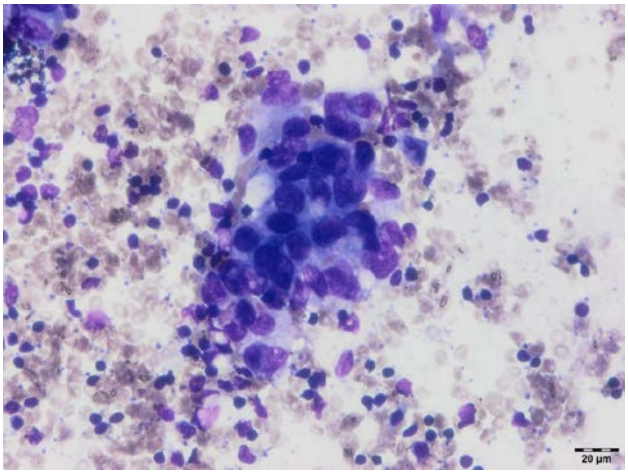


Fig. 4 – Cytologically diagnosed non-small cell lung cancer with histopathological prostate adenocarcinoma diagnosis (May Grunwald-Giemsa stain, ×400).

Concordance between cytological and histopathological diagnoses of surgical specimens was 61.48%. Unlike it, the concordance between histopathologic diagnoses of small biopsy specimens and surgical specimens was 95.2%.

There was neither statistically significant difference between cytological diagnosis and histopathological diagnoses of small biopsy specimens ($p = 0.856$) nor between cytological diagnosis and histopathological diagnoses of surgical specimens ($p = 0.196$). In addition, there was no statistically significant difference between histopathological diagnoses of small biopsies and surgical specimens ($p = 0.230$). Discordance in cytological, small biopsies, and histopathological diagnoses based on surgical specimens are presented in Table 1.

There was a statistically significant difference between diagnoses on cytological specimens, depending on the method of sampling ($p = 0.001$). There was statistically significantly less discordance in cytological diagnoses on material sampled by TBNA with histopathological diagnoses. Discordance in cytological and histopathological diagnoses on surgical specimens, depending on the cytological sampling method, is presented in Table 1.

Table 1

Discordance between cytological diagnoses and histopathological diagnoses on small biopsies and surgical specimens based on the method of sampling

Cytological diagnosis	Small biopsy histopathological diagnosis	Surgical specimen histopathological diagnosis	Sampling method for cytology
NSCLC	NSCLC	giant cell carcinoma	brush
NSCLC	undifferentiated carcinoma	carcinosarcoma	TBNA
NSCLC	NSCLC	large cell neuroendocrine tumor	TBNA
NSCLC	NSCLC	epithelial mesothelioma	brush
NSCLC	plasmacytoma	plasmacytoma	brush
NSCLC	NSCLC	sarcomatoid carcinoma	brush
NSCLC	NSCLC	anaplastic carcinoma	TBNA
NSCLC	prostate adenocarcinoma	prostate adenocarcinoma	TBNA
NSCLC	Non-Hodgkin lymphoma	Non-Hodgkin lymphoma	TBNA
NSCLC	Non-Hodgkin lymphoma	Non-Hodgkin lymphoma	TBNA
NSCLC	NSCLC	germ cell tumor	brush
squamous cell carcinoma	squamous cell carcinoma	mucoepidermoid carcinoma	brush

NSCLC – non-small cell lung cancer; TBNA – transbronchial needle aspiration.

In our study, sensitivity, specificity, positive and negative prognostic value, and accuracy of cytology as a diagnostic method were 94.98%, 98.60%, 95.72%, 98.35%, and 97.71%, respectively.

Discussion

Lung cancer is the most common cause of morbidity and mortality worldwide [10]. The highest incidence of lung cancer is in the ages between 65 and 74, on average 70 [11]. Patients in this study were slightly younger, with an average age of 60 for female and 63 for male patients. The youngest was a 39-year-old patient, similar to data in previous investigations [12]. Although the gender distribution of lung cancer patients is equal in developed countries, there were three times more male than female patients in this study, as was the case in other developing countries [10, 11, 13, 14].

An adequate sample for cytological and histopathological analysis has been obtained during bronchoscopy. The sample is fundamental for evaluation, confirmation, and in some cases, staging of tumor visualized during bronchoscopy [15]. The accuracy of diagnostic methods depends on the location of the tumor, its dimensions, type, and technical aspects, including the level of bronchoscopists' and pathologists' experience. Cytological diagnosis during bronchoscopy is preferable in centrally localized tumors, unlike tumors localized at the periphery of the lung when transbronchial biopsy, TBNA, or transthoracic biopsy should be done [16].

As it was in other studies worldwide, 26.63% of our patients had been diagnosed with squamous cell carcinoma based on cytomorphological criteria. Squamous cell carcinoma has been diagnosed in 46.75% of patients on small biopsy material, and all the diagnoses were confirmed on surgical specimens. The reason for fewer patients with cytologically diagnosed squamous cell carcinoma was poor differentiation of squamous cell carcinoma in approximately half of the patients. Those patients were diagnosed with NSCLC cytologically and needed further immunostaining for a more precise histopathological diagnosis [12, 17, 18].

In spite of 45.56% of lung adenocarcinoma histopathologically diagnosed on small biopsies material and confirmed on a surgical specimen, only 13.02% of lung adenocarcinoma were cytologically diagnosed. Similar results, with a small number of cytologically diagnosed lung adenocarcinoma in patients, were obtained in other studies [18, 19]. The majority of histopathologically diagnosed adenocarcinoma were cytologically diagnosed as NSCLC because of the lack of cytomorphological specific features significant for adenocarcinoma diagnosis according to the newest WHO 2015 criteria [4].

Besides the lack of cytomorphological characteristics for cytological adenocarcinoma diagnosis, a small number of viable cells, large amount of necrosis, tumor heterogeneity, and artifacts could also cause misdiagnosis [19, 20]. The precise diagnosis of adenocarcinoma on the cytological specimen is very important because of novel diagnostic methods. More cell blocks with paraffin-embedded cytological material and the possibility of further immunostaining are made from a part or from the rest of the cytological material. Furthermore, the necessity of cell viability for novel diagnostic methods is another advantage for cytological diagnosis [2, 8, 21]. In our study, the concordance of cytological and histopathological diagnosis was 61.48%, as was reported in the literature [12, 19, 21, 22]. There was a less statistically significant difference between cytological and histopathological diagnoses af-

ter sampling by the TBNA method in both our and other research. TBNA sampled material for cytological diagnosis is more abundant, better preserved, with more viable cells and less necrotic parts [12].

Avoiding diagnostic mistakes is very important because false positive diagnoses could lead to disease and even death. False negative diagnoses could, on the other hand, postpone earlier diagnosis and therapy [23]. Precise cytological diagnosis without immunostaining in poorly differentiated cancer is very difficult, as it was in our study. Cytologically misdiagnosed NSCLC in our study were later histopathologically diagnosed as large cell carcinoma, large cell neuroendocrine carcinoma, carcinosarcoma, epithelioid mesothelioma, Non-Hodgkin lymphoma, germ cell tumor, and plasmacytoma. According to the newest WHO recommendations, large cell carcinoma should not be diagnosed on cytological and small biopsies specimens [4]. Neuroendocrine characteristics are sometimes difficult to visualize during cytological diagnosing. Despite large single cells that can be seen in the majority of cytologically diagnosed Non-Hodgkin lymphoma, sometimes, because of material preservation, diagnosis can be a challenge [23].

Cytologically diagnosed lung adenocarcinoma, which was histopathologically diagnosed as metastatic prostate adenocarcinoma, was among cytological misdiagnoses in our study. Differencing primary and metastatic adenocarcinoma is necessary for cancer staging and adequate therapy. Without a patient's history and radiological findings, sometimes it is very difficult to do it only based on cytomorphological characteristics, as it was in our study [23, 24].

After cytologically diagnosed squamous cell carcinoma, histopathological diagnosis in one patient was mucoepidermoid carcinoma. Cytological smear contained only of necrotic background and squamous component – single cells and cluster of cells with basophilic cytoplasm, increased nucleocytoplasmic ratio, with an enlarged nucleus, without nuclei. Neither intermediate nor vacuolated cells, necessary for mucoepidermoid carcinoma diagnosis, did not exist on smear [25].

In our study, sensitivity, specificity, positive and negative prognostic value, and accuracy of cytology as a diagnostic method for lung cancer were 94.98%, 98.60%, 95.72%, 98.35%, and 97.71%, respectively. These results are similar to other results worldwide. In research by Tomar et al. [17], sensitivity, specificity, and positive and negative prognostic values of cytology were 88.88%, 100%, 100%, and 36.36%, respectively, in diagnostic material sampled by fine-needle aspiration and 65.07%, 75%, 97.61%, and 12%, respectively, in diagnostic material sampled by brush biopsy [17]. In the investigations of Ghildiyal et al. [13] and Pavani et al. [14], sensitivity, specificity, and positive and negative prognostic values of cytology as a diagnostic method in both neoplastic and non-neoplastic lesions were around 90%. Lower sensitivity was found in a few studies, including Gaur et al. [12], where it was 62%.

Conclusion

Cytological diagnosis of lung cancer is accurate, with high sensitivity and specificity. Even though there was some discordance between cytological and histopathologic diagnosis of NSCLC, it was not statistically significant. The value of cytology is high because less material and less time are needed for diagnosis, which is very important in advanced inoperable stages of diseases.

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Received on June 18, 2020
Revised on October 19, 2020
Accepted on November 4, 2020
Online First November, 2020