International Journal of Medical Science and Clinical Invention 9(1): 5800-5907, 2022
DOI:10.18535/ijmsci/v9i01.03
https://valleyinternational.net/index.php/ijmsci

Research Article,

Evaluation of P40 and Napsin A in the Differential Diagnosis of Non Small Cell Bronchogenic Carcinoma on Small Lung Biopsies

Dr. Savita Singh[1], Dr. Kuldeep Singh[2]

[1]Assistant professor RAMA medical college Kanpur
[2]Associate professor GSVM medical college Kanpur

Abstract:

Background: - Lung cancer is the leading cause of cancer-related mortality over word wide, although the pathological diagnosis of lung carcinoma is limited as only small specimen available for diagnosis.the availability of targeted therapies has created a need for precise subtyping of non-small cell lung carcinoma. Several recent studies have demonstrated that the use of Immunohistochemical markers can be helpful in differentiating lung squamous cell carcinoma (LSCC) from lung adenocarcinoma (LAC) not on surgically resected material but also on small biopsy samples and cytology.

Aim (1)To classify the non small cell lung carcinoma into major categories like squamous cell carcinoma (LSCC) and adenocarcinoma (LAC) and other categories by applying immunohistochemicalmarker like p40 (truncated p63) and Napsin A

(2)To analyse the sensitivity and specificity of p40 and Napsin A in light of histomorphology and/or other relevant immunohistochemical markers available, using appropriate statistical tests.

Material and methods:- This study was a one and half year (18 months) prospective study from Jan 2017 to June 2018, conducted in department of pathology on patients attending the outpatient and inpatient department of TB and respiratory disease, a total of 210 bronchoscopic guided biopsies / transthoracic (CT/MRI /guided) small tissue biopsies from the patients suspected of lung malignancy were incorporated in the study. 20 corresponding resection specimens (wedge resection and lobectomy) were also included in the study for correlation of morphology and immunohistochemical findings on small biopsies.

Results:-In our study IHC for both p40 and napsin –A aided in subtyping of 71.9% cases of non small cell lung carcinoma and this diagnostic accuracy was found to be statistically significant with p-value < 0.05.,on statistical analysis we found that napsin-A had a sensitivity of 90% and specificity of 80%. Also, positive predictive value and negative predictive value were seen to be 88.0% and 81.8% respectively.

Keywords: adenocarcinoma; cytology; napsin A; non small cell lung carcinoma; p40; small lung biopsy Squamous cell carcinoma.

Introduction:

Lung cancer is the leading cause of cancer-related mortality, accounting for over 150,000 death per year in the united states and over 1.3 million death word wide **[1,2].** Although the pathological diagnosis of resected samples is comparatively easy for patients with lung squamous cell carcinoma (LSCC) and lung adenocarcinoma (LAC), in most of the patients there are often only small specimen available for diagnosis. A Confirmed diagnosis solely dependent on bronchoscopic biopsy is impractical since the fiberoptic bronchoscopy guided biopsies are too small **[3].**

Primary lung carcinomas have been classified into small cell lung carcinomas (SCLC) and non-small cell lung carcinomas (NSCLC), the later include adenocarcinoma accounting for (50 to 70)% of total cases and squamous cell carcinoma (20-30)% and other subtypes (<10%) **[4,5].**

Recent advances in the treatment and molecular

diagnosis of non-small cell lung cancer (NSCLC) have made it critical for pathologists to distinguish between the 2 major histologic subtypes: adenocarcinoma (ACA) and squa-mouscell carcinoma (SQCC)

Materials and methods:

The present study was a one and half year (18 months) prospective study from Jan 2017 to June 2018, conducted in department of pathology on patients attending the outpatient and inpatient department of TB and respiratory disease, Jawaharlal Nehru Medical College and Hospital, AMU Aligarh. After obtaining all relevant clinical data, a total of two hundred ten (210) bronchoscopic guided biopsies / transthoracic (CT/MRI /guided) small tissue biopsies from the patients suspected of lung malignancy were incorporated in the study. Only histopathologically diagnosed lung malignancy as non-small cell primary lung carcinoma (NSCLC), which had sufficient tissue for IHC studies (p40 and napsin-A) were taken into account. In addition, 20 corresponding resection specimens (wedge resection and lobectomy) were also included in the study for correlation of morphology and immunohistochemical findings on small biopsies.

Exclusion criteria:-

•Histopathologically diagnosed Small cell bronchogenic carcinoma were excluded from the study.

•Those cases with Secondaries lung were excluded from the study.

Thus the study group comprised of 116 cases of histopathologically diagnosed non small cell lung carcinoma, and 20 cases of resection specimens. IHC for p40 and napsin-A was applied on total 72(62%).

Napsin-A: - Positive control – type II pneumocytes
Negative control- colon (no staining seen in columnar epithelium)

p40:- Positive control – normal skin tissue
Negative control- breast carcinoma

Interpretation of immunohistochemistry

1. The results of IHC showed Positive nuclear staining for p40 (truncated p63), and cytoplasm staining for napsin-A was recorded according to standardized guidelines. Immunoreactivity was read semiquantitatively on a scale from negative to 3+,

Tumors were considered negative if staining was completely absent or less than 10% in the relevant cells similar to the studies conducted by **[3].**

1+ cases was assigned if immunoreactivity was present in 10 to 25% neoplastic cells seen.
2+ cases was assigned if immunoreactivity was present in 26 to 50% neoplastic cells seen.
3+ cases was assigned if immunoreactivity was present in 51 to 100% neoplastic cells seen **[3].**

Statistical analysis

Statistical analysis was carried out using SPSS software (v.18.0). Chi-square test used to evaluate the significance, with a threshold of less than 0.05 was considered to be statistically significant.

Results:

Immunohistochemical Analysis of P40 in Various Histological Types of Non Small Cell Lung Carcinoma (Nsclc)

Out of 116 cases of NSCLC we took a total of 72 representative cases for p40 immunostaining irrespective of their histological subtypes. These 72 representative cases comprised of 10/31 cases of squamous cell carcinoma, which showed clear intercellular bridging and keratinization, and 10/22 cases of adenocarcinoma which showed well defined glandular area/or mucin production on histopathology. The major chunk comprised of 48/57 cases of poorly differentiated carcinoma (NOS). Two cases each of large cell carcinoma and adenosquamous carcinoma were also included.

Table 1: Histomorphological Types Of Non Small Cell Lung Carcinomas (N=116)

0	Types of NSCLC (n=116)	Number of cases (116)	Percentage (%)
1	Squamous cell carcinoma	31	26.7
2	Adenocarcinoma	22	19.0

3	Large-cell carcinomas	4	3.4
4	Adenosquamous carcinoma	2	1.7
5	Poorly differentiated carcinoma(NOS)	57	49.0

Table 2: Immunohistochemical Analysis of P40 in Various Histological Types of Non Small Cell Lung Carcinoma (N= 72)

Tumour type	Number of cases stained for p40	Numberof cases exhibiting P40 staining (%)			
		-ve	1+	2+	3+
Squamous cell carcinoma (n=31)	10		2(20%)	2(20%)	6(60%)
Adenocarcinoma(n=22)	10	9(90%)	1(10%)	_	_
Large cell carcinoma (n=4)	2	2(100%)	_	_	_
Adenosquamous carcinoma (n=2)	2	-	-	1(50%)	1(50%)
Poorly differentiated carcinoma (NOS) (n=57)	48	20(42%)	8(17%)	12(25%)	8(17%)
Total	72	31(43.0%)	11(15.3%)	15(21.0%)	15(21%)

Table 3: Immunohistochemical Analysis of Napsin-A in Various Histological Types of Non Small Cell Lung Carcinoma (N=72)

Tumour type	Number of cases stained for NAPSIN-A	Number of cases exhibiting NAPSIN –A staining (%)			
		-ve	1+	2+	3+
Squamous cell carcinoma (n=26)	10	8(80%)	2(20%)	_	_
Adenocarcinoma(n=21)	10	1(10%)	2(20%)	5(50%)	2(20%)
Large cell carcinoma (n=2)	2	2(100%)	_	_	_
Adenosquamous carcinoma (n=1)	2	_	1(50%)	1(50%)	_
Poorly differentiated carcinoma (NOS) (n=57)	48	29(60.4%)	7(14.6%)	9(18.7%)	3(6.2%)
Total	72	40(55.5%)	12(16.6%)	15(21%)	5(7.0)

Comparative Assessment of P40 Nuclear Marker and Cytoplasmic Napsin-A in Various Histological Types of Non Small Cell Lung Carcinoma (N=72)

Table 4: Analysis of Cases Based On both P40 and Napsin-A (N=72)

Tumour type	Number of cases stained for both p40, NAPSIN-A (n=72)	p40 (n=72)		NAPSIN –A (n=72)	
		Positive IHC(%)	Negative IHC (%)	Positive IHC (%)	Negative IHC (%)
Squamous cell (SCC) carcinoma (n=31)	10	10(100%)	_	2(20%)	8(80%)
Adenocarcinoma (ADC) (n=22)	10	1(10%)	9(90%)	9(90%)	1(10%)
Large cell carcinoma (n=4)	2	_	2(100%)	_	2(100%)

Adenosquamous carcinoma (n=2)	2	2(100%)	_	2(100%)	_
Poorly differentiated Carcinoma (NOS) (n=57) PD-CA(NOS)	48	25(52.1%)	16(33.3%)	16(33.3%)	25(52.1%)
Total	72	38(52.7%)	27(37.5%)	29(40.2%)	36(50%)

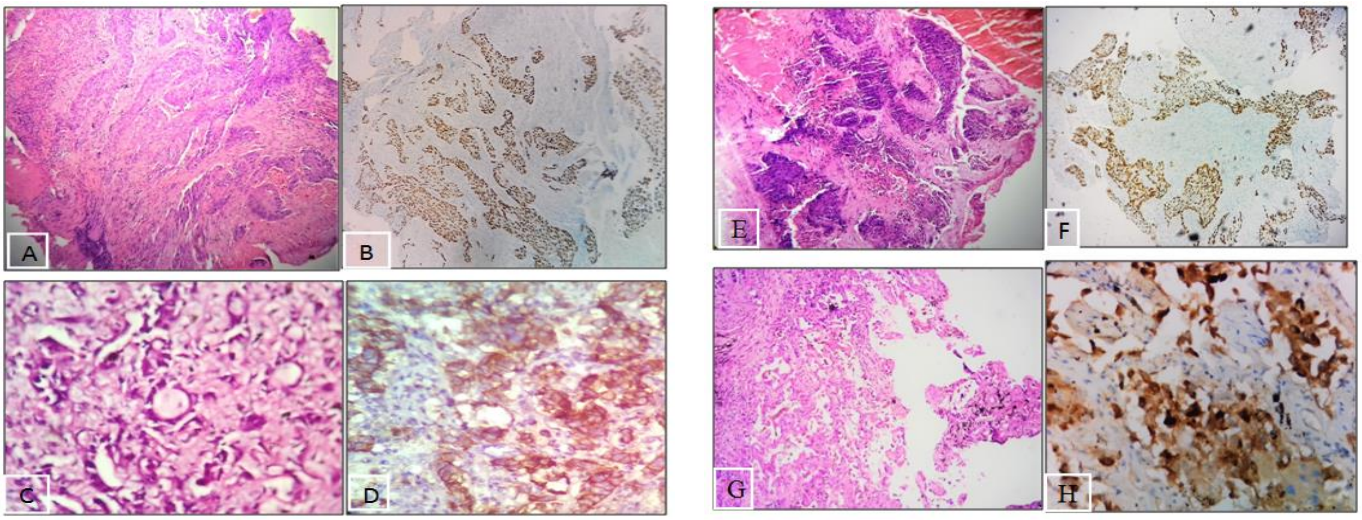

Figure
A- Moderately differentiated Squamous cell carcinoma lung- Biopsy shows intercellular junctions and keratinized malignant squamous cells (H&E x 40).
B- Moderately differentiated Squamous cell carcinoma- p40 shows strong (3+) nuclear positivity (p40 IHC x 10).
C-Moderately Differentiated Adenocarcinoma lung – biopsy shows malignant cells with glandular pattern (H &E x 40).
D-Moderately differentiatedadenocarcinoma- Napsin-A shows moderate (2+) cytoplasmic immunoreactivity (Napsin-A IHC x 40).

Figure
E: Poorly differentiated carcinoma (NOS) lung- Biopsy shows sheets of atypical cells (H&E x 10).
F - Poorly differentiated carcinoma (NOS) showing p40 3+ nuclear immunoreactivity. Napsin-A was negative.this case was diagnosed finally as SCC after IHC (p40 IHC x 10),
G - poorly differentiated carcinoma (NOS) lung- Biopsy show small clusters and singly scattered atypical cells on (H&E x 10),
H - Poorly differentiated carcinoma (NOS) showing Napsin –A cytoplasmic 2+ immunoreactivity. Diagnosed finally as adenocarcinoma after IHC (Napsin-A IHC x 40).

Resection specimens:- Corresponding resection specimens (wedge resection and lobectomy) were available in 20 cases of NSCLC, hence these cases were also included in present study for correlation of morphology and immunohistochemical results.

Table 4: Correlation of Immunohistochemical Diagnosis On Small Biopsies With Final Diagnosis On Surgical Specimens (N=20)

Diagnosis on resection specimen		**Original diagnosis on biopsy after p40 and napsin-A**		
Types of diagnosis	**Number of cases (n=20)**	**Adenocarcinoma ADC**	**Squamous cell carcinoma SCC**	**PD-CA(NOS)**
SCC	11		10	1
ADC	6	5	1	-
Adenosquamous Carcinoma	2	-	2	-
Sarcomatoid carcinoma	1	-	-	1

ADC-Adenocarcinoma, SCC- Squamous cell carcinoma, PD-CA (NOS) –poorly differentiated carcinomaell with final diagnosis made on resection specimens in 17 of 20 cases. Two case classified as squamous cell carcinoma on small biopsy turned out to be adenosquamous (Figure J) on surgical specimen while the other one cases diagnosed as squamous cell carcinoma on biopsy was turned out to be adenocarcinoma on resected specimen.rest two case of poorly differentiated carcinoma (NOS) was reclassified as squamous cell carcinoma and sarcomatoid carcinoma on resected specimen.

Out of 6 cases of adenocarcinomas on resection specimen 3 were acinar predominant and 2 were invasive mucinous adenocarcinoma (Figure I), while 1 case was lepidic predominant Aden

Original diagnosis and immunohistochemical profile on small biopsies correlated w ocarcinoma (Figure K) Squamous cell carcinomas were keratinizing type in 10 cases, while single case of squamous cell carcinoma showed basaloid morphology on resection specimen.

Thus the diagnosis on biopsies correlated well with the diagnosis on resected specimens in 85% cases.

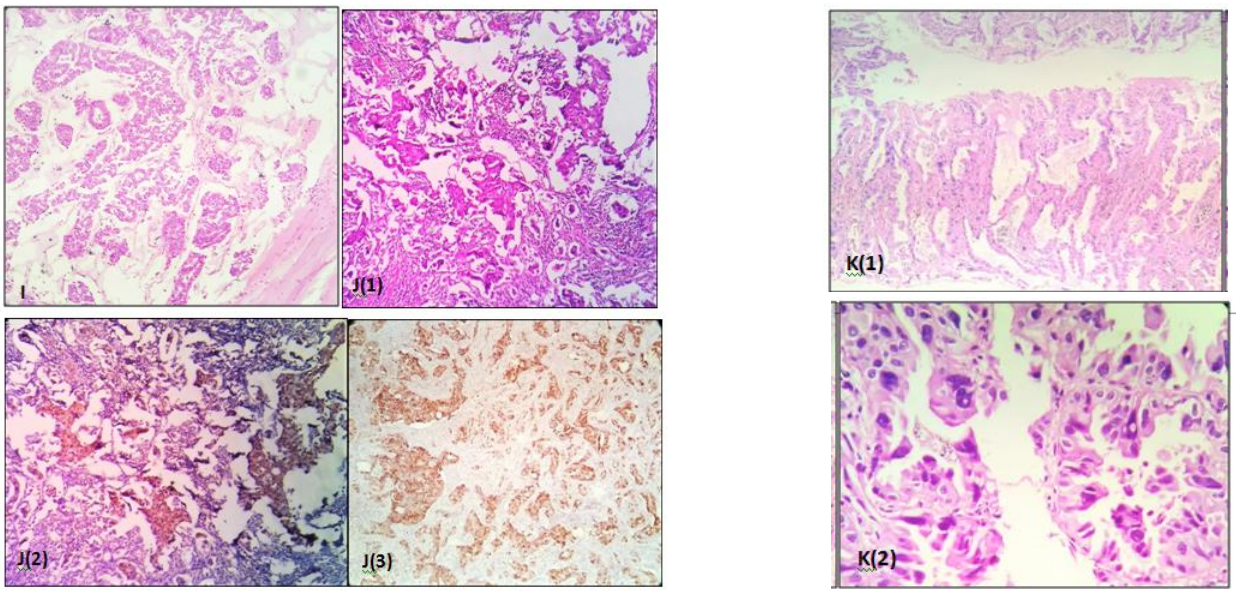

Figure I: Mucinous adenocarcinoma lung-resection shows well formedglandular element with mucin production (H&E x 10). Figure J(1)Adenosquamous carcinoma lung- biopsy shows both squamous and glandular component (H&E x 10). Figure J(2)Adenosquamous carcinoma lung- biopsy shows p40 nuclear 2+ immunoreactivity in squamous component (p40 IHC x 10). Figure J (3) Adenosquamous carcinoma lung- biopsy shows cytoplasmic 2+ to 3+ immunoreactivity in glandular component (Napsin-A IHC x 10).

Figure K (1);-Lepidic predominant adenocarcinoma- Resection shows lepidic pattern of malignant cells lining the alveoli (H&E x 10).Figure K (2): Lepidic predominant adenocarcinoma- resection shows lepidic pattern of highly atypical cells (H&E x 40).

Table 5: Comparative Histopathological and Immunohistochemical Analysis of Various Histological Types of Non Small Cell Lung Cancer (N=72)

Histopathological diagnosis	Number of cases stained (n=72)	p40 positivity (n=72)	napsin-A positivity (n=72)	Final diagnosis after IHC	Any change in diagnosis
Squamous cell carcinoma (n=31)	10	9(90%) (p40+/napsin-A-)	1*(10%) (p40+/napsin-A+)	9cases-SCC 1*cases- Inconclusive	Yes 1/10 cases
Adenocarcinoma (n=22)	10	2**(20%) (p40+/napsin-A-)	8(80%) (p40-/napsin-A+)	8cases-ADC 2**cases- SCC	Yes 2/10 case
Large cell carcinoma (n=4)	2	_	_	Large cell carcinoma	No

Adenosquamous carcinoma (n=2)	2	2(100%) (in squamoid area)	2(100%) (in glandular area)	Adenosquamous carcinoma	No
Poorly differentiated Carcinoma (NOS) (n=57)	48	25(52.1%)	16(33.33%)	25 cases SCC(p40+/napsin-A-)	Yes
				16 cases-ADC(p40-/napsin-A+)	
				7cases-PDCA(NOS)***	
Total	72				

ADC-Adenocarcinoma, SCC- Squamous cell carcinoma, PD-CA (NOS)-poorly differentiated carcinoma

(* diagnosed as Squamous cell carcinoma on resected specimen
** diagnosed as adenosquamous carcinoma on resected specimen (Fig J)
*** 7 cases could not be subclassified because of p40+/napsin-A+ status in 3 and p40-/napsin-A- in 4 cases

Diagnostic accuracy of p40 and napsin-A:-

On performing the statistical analysis of p40 immunoexpression in diagnosing lung squamous cell carcinoma, we found that p40 had a sensitivity of 80% and specificity of 90%. Also, positive predictive value and negative predictive value were seen to be 81.8% and 88.9% respectively. On performing the statistical analysis of napsin-A immunoexpression in diagnosing lung adenocarcinoma, we found that napsin-A had a sensitivity of 90% and specificity of 80%. Also, positive predictive value and negative predictive value were seen to be 88.9% and 81.8% respectively. Overall, the role of p40 and napsin-A immune-reactivity was found to be statistically significant (p-value of <0.05) in categorizing the subtypes of NSCLCs.

Discussion:

In NSCLC maximum cases belonged to poorly differentiated carcinoma not otherwise specified (NOS) i.e 57 cases (49%), followed by squamous cell carcinoma and adenocarcinoma accounting for 31 (26.7%) and 22(19%) cases respectively. Other entities were large cell carcinoma and adenosquamous carcinoma which comprised of small number of cases. Similar to our observation in a recent study conducted by **[6.7].**NSCLC comprised approximately of 80-85% of all lung cancers. Similar study had also been conducted by **[8, 9]** which showed that Small cell lung cancer (SCLC) accounts for 15% of lung cancer cases and Non–small cell lung cancer (NSCLC) accounts for the remaining 85% of cases which is further divided into 3 major pathologic subtypes: adenocarcinoma, squamous cell carcinoma, and large cell carcinoma

Age:-

In our study age of lung cancer patients ranged from 30 to 89 years with a mean age of 65 years. Our study was in concordance with the study by **[10]** which was done on 827 patients where the mean age was 67.5 years. According to **[11]** the average age of lung cancer diagnosis is at the age of 70, which is again in agreement with our observation.

IHC for both p40 and napsin –A aided in subtyping of 71.9% cases of non small cell lung carcinoma as adenocarcinoma, squamous cell carcinoma, and other major subcatogries (adenosquamous carcinoma and large cell carcinoma).In our study p40 immunoexpression was seen in 10/10 cases(100%) of squamous cell carcinoma and 28/48 cases(58.3%) in poorly differentiated carcinoma and napsin-A in 9/10 cases (90%) of adenocarcinoma and 19/48 cases (39.6%) poorly differentiated carcinoma-NOS. Similar results were also seen by **[12]** who also used p40 and napsin-A antibodies on NSCLC and accurately subtyped 88.8% of tumors on a single slide as adenocarcinoma, squamous cell carcinoma. Similar study was also conducted by **[20]** she studied the effectiveness of a minimal panel of antibodies comprising of p40 and TTF-1 in subclassification of NSCLC,

Studies	p40		napsin-A	
	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)

Sun et al., (2014)	100	95.54	76.4	100
Walia et al., (2017)	100	100	_	_
Present study (2018)	80	90	90	80

In our study we evaluated the ability of a 2-antibodies targeting napsin A and p40 to subtype NSCLC on the same histologic section. The sensitivity and specificity of p40 was 80%, 90% and, of napsin-A was 90%, 80% for adenocarcinoma and squamous cell carcinoma respectively Many authors have advocated antibody panels to enhance the sensitivity and specificity of NSCLC subtyping **[13,14,15,16,17].** Our findings were in accordance with the observation of **[20]** who also calculated that p40 showed 100 percent sensitivity and specificity for squamous differentiation. In a significant study conducted by **[3].** it was found that Positive expression of p40 (ΔNp63) was observed in 100% of patients with lung squamous cell carcinoma, but immunoexpression of napsin A was noted in 78.98% of patients with lung adenocarcinoma. The sensitivity and specificity of p40 (ΔNp63) were 100% and 95.54%, respectively in the diagnosis of lung squamous cell carcinoma, and those of combined TTF1 and napsin A were 76.43% and 100%, respectively, in the diagnosis of lung adenocarcinoma. Many studies have utilized three or more markers for subclassification and have found a similar diagnostic rate as observed in our study. **[18,19].** In contrast to them we have used only two markers In our study the diagnosis on resected specimens correlated well with the diagnosis on biopsies in 85% cases. Two cases however missed the diagnosis on small biopsy probably because of sampling error.Similar results were also seen in study conducted by **[20].**

To conclude, we observed that the combined used of p40 and napsin-Aimmunostains on small lung biopsy helps greatly in categorizing the primary lung carcinoma especially poorly differentiated carcinoma (NOS- not otherwise specified) into the prognostically important subcategories of squamous cell carcinoma and adenocarcinomas. Also, based on conclusion drawn from previous studies, we believe that, p40 and napsin-A are specific and sensitive for squamous cell carcinoma and adenocarcinoma respectively.

Conclusion:

Napsin-A had a sensitivity of 90% and specificity of 80%. Also, positive predictive value and negative predictive value were seen to be 88.0% and 81.8% respectively.

This study emphasizes that the combined used of p40 and napsin-Aimmunostains on small lung biopsy helps greatly in categorizing the primary lung carcinoma especially poorly differentiated carcinoma (NOS- not otherwise specified) into the prognostically important subcategories of squamous cell carcinoma and adenocarcinomas. Apart from being fairly sensitive and specific use of these two immunostains obviates the need of more immunomarkers, thus helps saving the small tissue for molecular study if needed

Bibliography:

[1] Edge S, Compton C. The American Joint Committee on Cancer: the 7th Edition of the AJCC Cancer Staging Manual and the Future of TNM. Ann of SurgOncol 2010;17(6):1471-74.

[2] Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA: Cancer J Clin. 2014;64(1):9-29.

[3] Sun TI, Xie HO, Kong L. Role of p40 (ΔNP63), p63, thyroid transcritpion factor-1 and Napsin A in differential diagnosis between lung squamous cell carcinoma and lung adenocarcinoma. Acta Med Mediterr. 2014;30:923-27.

[4] Travis WD, Brambilla E, Müller-Hermelink HK, Harris CC. Pathology and Genetics: Tumours of the Lung, Pleura, Thymus and Heart. Lyon: IARC, 2004.

[5] Travis WD, Brambilla E, Noguchi M, Nicholson AG, Geisinger KR, Yatabe Y, Beer DG, Powell CA, Riely GJ, Van Schil PE, Garg K. International association for the study of lung cancer/american thoracic society/european respiratory society international multidisciplinary classification of lung adenocarcinoma. J ThoracOncol. 2011;6(2):244-85.

[6] Travis WD, Brambilla E, Burke AP, Marx A, Nicholson AG. Introduction to the 2015 World Health Organization classification of tumors of the lung, pleura, thymus, and heart. J ThoracOncol. 2015;10(9):1240-2.

[7] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin. (2017).

[8] Herbst R, Heymach J, Lippman S. Lung Cancer. New Engl J Med. 2008;359(13):1367-80.

[9] Howlader N. SEER cancer statistics review, 1975-2008. http://seer. Cancer. Gov/csr/1975_2008/. 2011.

[10] Shah PL, Singh S, Bower M, Livni N, Padley S, Nicholson AG. The role of transbronchial fine needle aspiration in an integrated care pathway for the assessment of patients with suspected lung cancer. J ThoracOncol 2006;1(4):324-27.

[11] Malvezzi M, Bosetti C, Rosso T, Bertuccio P, Chatenoud L, Levi F, Romano C, Negri E, La Vecchia C. Lung cancer mortality in European men: trends and predictions. Lung Cancer. 2013 ;80(2):138-45.

[12] Nishino M, Hoang MP, Della Pelle P, Morales-Oyarvide V, Huynh TG, Mark EJ, Mino-Kenudson M. Napsin A/p40 antibody cocktail for subtyping non-small cell lung carcinoma on cytology and small biopsy specimens. Cancer cytopathol 2016;124(7):472-84.

[13] Mukhopadhyay S, Katzenstein AL. Subclassification of non-small cell lung carcinomas lacking morphologic differentiation on biopsy specimens: utility of an immunohistochemical panel containing TTF-1, napsin A, p63, and CK5/6. The Am J SurgPathol. 2011;35(1):15-25.

[14] Tsuta K, Tanabe Y, Yoshida A, et al. Utility of 10 immunohistochemical markers including novel markers (desmocollin-3, glypican 3, S100A2, S100A7, and Sox-2) for differential diagnosis of squamous cell carcinoma from adenocarcinoma of the lung. J ThoracOncol. 2011;6:1190-99.

[15] Pelosi G, Fabbri A, Bianchi F, Maisonneuve P, Rossi G, Barbareschi M, Graziano P, Cavazza A, Rekhtman N, Pastorino U, Scanagatta P. ΔNp63 (p40) and thyroid transcription factor-1 immunoreactivity on small biopsies or cellblocks for typing non-small cell lung cancer: a novel two-hit, sparing-material approach. J ThoracOncol. 2012;7(2):281-90.

[16] Sterlacci W, Savic S, Schmid T, et al. Tissue-sparing application of the newly proposed IASLC/ATS/ERS classification of adenocarcinoma of the lung shows practical diagnostic and prognostic impact. Am J ClinPathol. 2012;137:946-56.

[17] Zachara-Szczakowski S, Verdun T, Churg A. Accuracy of classifying poorly differentiated non-small cell lung carcinoma biopsies with commonly used lung carcinoma markers. Hum Pathol. 2015;46:776-78.

[18] Koh J, Go H, Kim MY, Jeon YK, Chung JH, Chung DH. A comprehensive immunohistochemistry algorithm for the histological subtyping of small biopsies obtained from non-small cell lung cancers. Histopathology 2014;65:868-78.

[19] Zhao W, Wang H, Peng Y, Tian B, Peng L, Zhang DC. ΔNp63, CK5/6, TTF-1 and napsin A, a reliable panel to subtype non-small cell lung cancer in biopsy specimens. Int J ClinExpPathol 2014;7:4247-53.

[20] Walia R, Jain D, MadanK,et al.p40 & thyroid transcription factor-1 immunohistochemistry: a useful panel to characterize non-small cell lung carcinoma-not otherwise specified (NSCLC-NOS) category. Indian J Med Res.2017;146:42-48.