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ANTIGENIC PHENOTYPE OF LUNG CARCINOMAS: USUAL SPECTRUM OF DISTRIBUTION OF THYROID TRANSCRIPTION FACTOR-1, CYTOKERATIN 7, CYTOKERATIN 20, AND NEURON SPECIFIC ENOLASE – BASIC IMMUNOHISTOCHEMICAL STUDY OF 21 CASES

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Abstract

Immunohistochemistry (IHC), as such, can be used in routine pathology in order to make correct diagnosis of lung carcinomas. Consequently, more detailed analyses are needed in this field in order to make a wide spectrum of unique combinations for such pulmonary neoplasms. Our aim was to apply an antibody panel, and examine and confirm its utility in the differential diagnosis of lung cancer. Twenty-one cases (both bioptic and surgical material) of diagnosed lung cancer were investigated. An immunohistochemical analysis – (RTU FLEX Immunoperoxidase system) was made using Dako monoclonal antibodies (Cytokeratin 7, CK7; Cytokeratin 20, CK20; Neuron specific enolase, NSE, Thyroid transcription factor-1, TTF1 and Leucocyte common antigen, LCA). LCA expression was not expressed in any of our cases. Most adenocarcinoma were CK7(+) – 83.3% and TTF1(±) – 50%. The CK20(+) expression showed a metastatic pulmonary deposit of adenocarcinoma in the lung. TTF1(+) – 100%, NSE(+) – 100% and CK7(-) – 66.66% expression was found in most cases of SCLC. NSE(+) –100% had the highest expression in carcionoid tumour, while TTF1(+) expression was highest in SCLC. For squamous cell carcinoma (SqCC), immunostaining was negative for this antibody panel, except focal and weak expression of NSE – 60%, so we did some extra IHC using CKHMW antibody, which showed the highest expression. The essential antibody panel that we have confirmed and suggest for routine basic differential diagnosis of pulmonary neoplasms is: TTF1, CK7, CK20 and NSE. Due to the high number of co-occurrunces IHC should not be performed alone, but integrated in conjunction with morphological diagnosis.

Key words: immunohistochemistry, pulmonary neoplasms, antigen distribution, antibody panel.

Introduction

Malignant lung neoplasms represent one of the most serious problems in modern oncology, as well as the leading reason for death in the Western world, despite the fact that nowadays most of the cancerous factors are already well-known and classified, such as smoking [1–5].

The basic division of malignant lung neoplasms is into two large groups: small-cell lung carcinoma (SCLC) and non small-cell lung carcinoma (NSCLC). This division is significant because of the important differences in their biological and clinical behaviour [6]. Histological classification of lung neoplasms is based on the classification implemented by the World Health Organisation (WHO) in 1999, later shaped and upgraded with new molecular and clinical characteristics in 2004 [2, 7, 8].

The histological diagnosis can be observed through material obtained in different ways: with sputum cytology, thoracocentesis, lymph node biopsy, bronchoscopy, transthora-

cic fine needle biopsy, video aided thoracoscopy or thoracotomy [5].

Lung cancer morphology is quite complex, which makes getting the right and accurate diagnosis difficult. Consensus diagnostics, together with immunohistochemistry and molecular techniques, lead the way to safer, more detailed and more accurate diagnosis [9].

That is the reason why nowadays immunohistochemistry (IHC) is becoming more and more acknowledged, since it can detect the differentiation, especially regarding the histological heterogeneity of the lung neoplasms [10].

The need to apply the target therapy for NSCLC imposes even more the need for their more detailed further classification by immunohistochemical techniques [11].

In order to identify biological markers of malignant pulmonary neoplasms, IHC, as such, can be used in the routine pathology procedure [12].

The role of IHC is to recognize the antigens through the antibodies, and then to identify and classify the specific cells from the cellular population whose morphology is either heterogeneous or homogenous. The visualization of the complex antigen-antibody is possible with different techniques through previous marking of the antibody with fluorochrome conjugate or enzyme [13].

The study's objective is applying the basic diagnostic algorithm to determine the practical use of the immunohistochemical algorithms of the antibodies in differential diagnosis of lung neoplasms.

Materials and methods

The study is retrospective and was performed at the Institute of Pathology. The material was used in the period from 01.01.2012 to 31.12, using 2012, 21 bioptic samples and operative materials with diagnosed lung cancer. The microscopic evaluation was performed by two pathologists, independently of each other, and in the cases where it was different, a third experienced pathologist was consulted. The final diagnosis was made by consensus. The bioptic samples and the operative material were delivered from the University Thoracic and Vascular Surgery Clinic, the University Pulmonology Clinic at the Medical Faculty in Skopje and the Institute of Lung Diseases, Republic of Macedonia.

The samples were processed with the standard procedure for integrating in paraffin, while the paraffin sections were stained with hematoxylin & eosin (HE) and immunohistochemically with the standard immunohistochemical techniques (EnVision Flex PT link; DAKO, Denmark), the following panel of antibodies was used: thyroid transcription factor 1 [TTF-1], cytokeratin-7 [CK-7], cytokeratin-20 [CK-20], leucocyte common antigen [LCA], and neuron specific enolase [NSE]. In five of the total number of the cases, additional immunohistochemical staining was made for the following antibodies: CEA, CK AE1/AE3, Chromogranin, Synaptophysin, CKHMW, CK5/6, and CK 8. That was needed because of their poor tumour differentiation, determination of their neuroendocrine status, or problems in distinction between primary and secondary adenocarcinoma. Positive and negative controls were carried out and processed concurrently for each staining separately. Slides were stained using a streptavidin-biotin kit, and then they were evaluated semi-quantitatively.

Results

The patients in this research were between 31 and 78 years old (60.48 ± 10.78) when the surgery/biopsy was performed, of whom 15 were male and 6 female (Fig. 1). The resulting bioptic and operative materials were processed by standard procedure and had a suitable histopathological diagnosis. The following distribution of lung neoplasms was established: small-cell 3/21 (14.29%), non small-cell 13/21 (61.90%) and non other specified 5/21 (23.81%) (Fig. 2). There was a further histopathological classification for the non small-cell carcinomas: squamous-cell carcinoma 5/21 (23.81%), adenocarcinoma 6/21 (28.57%), large-cell carcinoma 2/21 (9.52%), small-cell carcinoma 3/14 (14.29%), non other specified 5/21 (23.81%) (Fig. 3). The slides were stained immunohistochemically with the following panel of antibodies: TTF-1, CK-7, CK-20, LCA, and then a percentage of structure for suitable distribution of every antibody in every lung neoplasm accordingly was calculatred. Results are shown in Table 1.

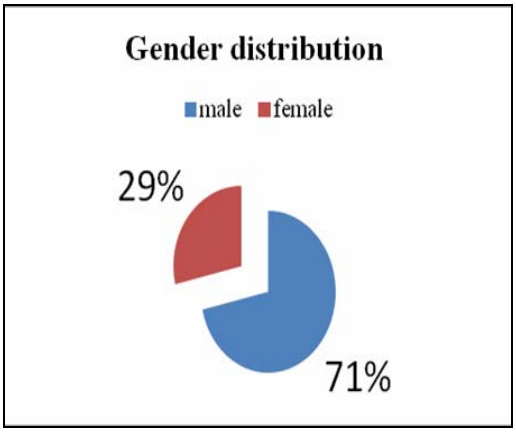

Figure 1 – Patients by gender distribution

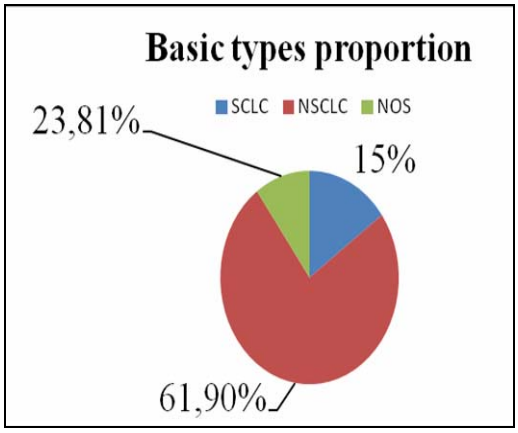

Figure 2 – Basic lung carcinoma type proportion

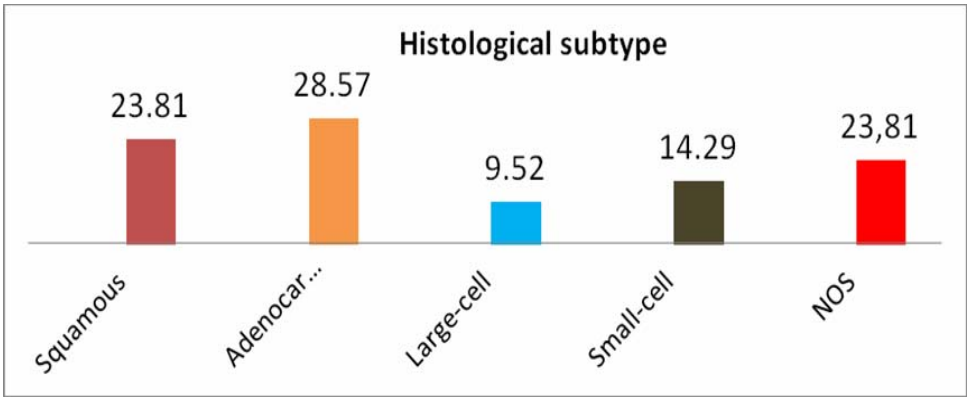

Figure 3 – Histological subtypes of lung carcinoma distribution

Table 1

Presentation of presence of singular antibodies specific for different entities of lung carcinoma

Tumour antibody	Tumour positivity (%)			
	Small-cell carcinoma (n = 3)	Non small-cell carcinomas (n = 13 + 5 NOS)		
		Squamous-cell carcinoma (n = 5)	Adenocarcinoma (n = 6)	Large-cell carcinoma (n = 2)
Thyroid transcription factor 1	100	0	50	50
Cytokeratin 7	66.66	20	83.3	100
Cytokeratin 20	33.33	0	16.66	0
Leucocyte common antigen	0	0	0	0
Neuron specific enolase	100	60	33.33	100

Positive expression of TTF-1, Fig. 4, was noticed in 50% of the adenocarcinomas and large-cell carcinomas. Its strongest expression was noticed in the small-cell carcinoma, namely in 100% of the cases.

CK-7, positivity Fig. 5, was variably sent in different cancer types; however, it was most present in adenocarcinomas, namely in 83.3% of the cases. NSE was present in the largest percentage in the small-cell carcinomas, namely in 3/3, 100%. A focal or weak presence was also noticed in other cancer types, and the strongest expression was present in the carcinoid tumour as well.

It is worth noting the data that CK-20 is negative in all lung neoplasms, except for its

only expression in the metastatic lung adenocarcinoma, which originates from the colon adenocarcinoma. The staining with LCA was absolutely absent in all of cases 0/21. Squamous-cell carcinomas have the poorest expression for all of the antibodies used, which imposes the fact that more specific stainings are needed to prove and confirm it, such as CKWS staining.

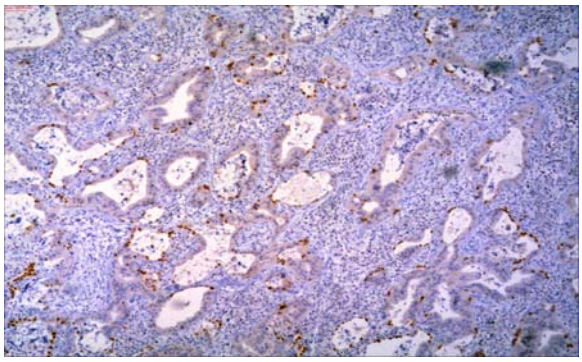

Figure 4 – Non Small-cell Lung Carcinoma. Immunohistochemistry TTF-1, maginification 500 x

In the Table 2 are shown additional stainings for appropriate antibodies, which further completed the immunohistochemical analysis in a certain small number of cases. These were combined with the basic panel TTF-1, CK7, CK20 and LCA. The additional stainings went in favour of the previously set working diagnosis with the primary staining of the above mentioned antibody panel.

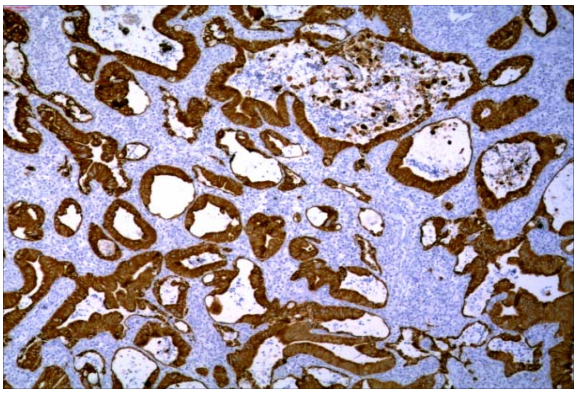

Figure 5 – Adenocarcinoma. Immunohistochemistry CK7, maginification 500 x

Figure 6 represents the algorithm of panel of antibodies related to the probable diagnosis which comes from its use. We suggest the same algorithm for basic orientation and setting a working diagnosis as a part of the histomorphological characteristics of tumour tissue. Additional immunohistochemical stainings are needed if the final look does not satisfy the basic criteria for setting an appropriate diagnosis, which will be discussed through further studies.

Table 2

Additional immunohistochemical staining in separate lung carcinomas with a different panel of antibodies

Tumour antibody	**Tumour positivity (%)**			
	Small-cell carcinoma (n = 1)	**Non small-cell carcinomas (n = 13 + 5 NOS)**		
		Squamous-cell carcinoma (n = 1)	**Adenocarcinoma (n = 2)**	**Carcinoid tumor (n = 1)**
Carcinoembryonic antigen	+	/	+++/-	/
Cytokeratin AE1/AE3	+	/	+	/
Chromogranin	+	-	-/-	+
Sunaptophysin	+++	-	-/-	-
CKWS	/	+++	/	/
Cytokeratin 5/6	/	/	-/-	/

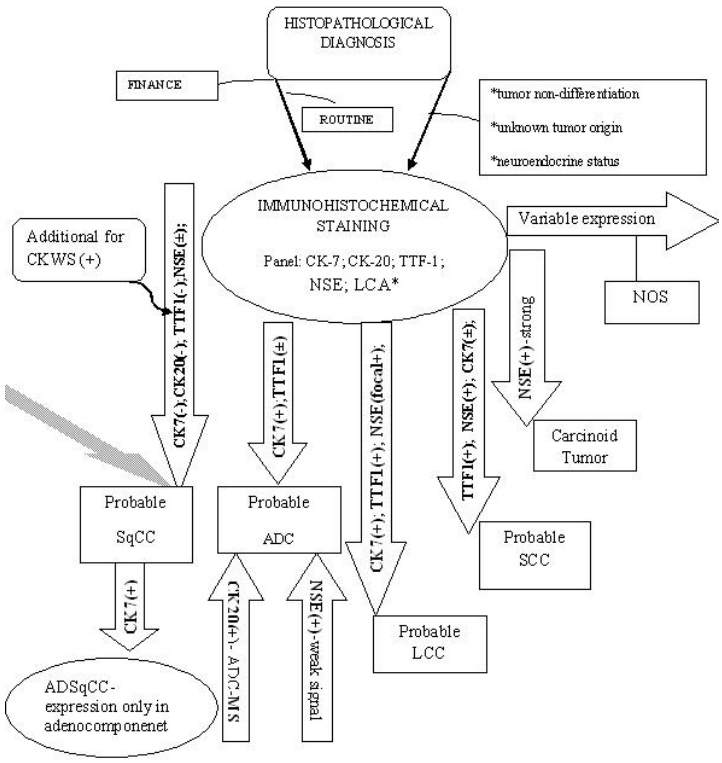

Figure 6 – Basic algorithm for differentiation of basic lung carcinomas

Discussion

Related lung cancer diagnosis significantly reduces the overall survival of the patients; therefore discovering the origin, the subtype of the lung cancer, is as crucial for diagnosis as it is for the prognosis [14].

Squamous-cell carcinoma is one of the most common types of lung cancer [15]. In the samples of this neoplasm type the complete absence of expression for TTF-1 and CK 20 was noticed, and in 1/5 cases there was a registered positivity for NSE. CK-7 is absent in all the cases, in fact its presence is noticed only in adenosquamous carcinoma, or, more accurately, positive expression corresponds to the glandular component. Staining with CKWS shows the squamous-cell component of the neoplasm. According to a review of the literature, the diagnosis of squamous-cell carcinoma most usually does not require immunohistochemical evaluation, however the absence of CK7 and CK20 is noticed [16]. In the study of Righi L et al., a positive correlation is established between squamous-cell carcinoma and the p63+/TTF1-phenotype [17]. Coexpression of p63 with CK5 indicates high sensitivity and 100% specificity for squamous-cell lung carcinoma [18]. The meaningful role that TTF-1 plays in the diagnosis and origin of adenocarcinomas cannot be used with the squamous-cell carcinomas as well, mainly because the majority are immunonegative for TTF-1 [19]. The CK5+ and TTF1- showings are in favour of most probable squamous-cell carcinoma [20].

In the adenocarcinomas in this study, a positive expression for CK-7 in 83.3% of the cases and variable expression for TTF1- in 50% of the cases is noticed. In 1/6 cases, a focal presence of NSE was noticed, and a moderately weak expression was detected in one more case. There are similar results in the research of Harlamert et al. as well, where the expression of TTF1- is positive in 76%, and for CK7 in 95% [21]. Positivity for CK7 is noticed in 97% of the samples in the study by Chhieng et al. [22]. Cytokeratin subsets as well as the more specific differential markers like TTF1- are extremely useful in distinguishing adenocarcinoma from other types of lung neoplasms [16]. The data state that TTF-1 as an immuno-

histochemical marker can be used to determine the origin of tumours, adenocarcinomas, (lungs and thyroid), as a highly specific tissue factor for them [23].

The review of numerous different studies indicated a positive correlation between adenocarcinomas and TTF1+ [17, 21, 24]

Also, the results of a study conducted by Tacha D, show that coexpression of TTF1- with Napsin A, is sensitive and highly specific for lung adenocarcinomas [18].

Namely, the lungs represent one of the most frequent areas of metastatic infiltration. In the study conducted on 170 samples of metastatic adenocarcinomas it was discovered that the majority (64%) of the primary neoplasms are TTF 1 positive, whereas adenocarcinomas which metastasized from the other organs are completely TTF 1 negative. This makes TTF 1 significant in determining primary and metastatic adenocarcinomas [19].

The presence of CK-20 in one of the cases in this study, as well as in studies in Taiwan [25] and Alabama [22], was in favour of metastatic lung adenocarcinoma.

It is noted that with immunohistochemical evaluation, adenocarcinomas most often show TTF-1+, CK7+, CK5- and p63-. However, there are exceptions where a variable presence of CK5, CK7 and p63 is confirmed [17].

The conducted immunohistochemistry shows positive expression for CK-7 in 2/2 samples in the large-cell type of lung carcinoma, whereas for NSE in foci a positive expression in 30% of the examined samples is noted. The literature reviewed indicates that this pathological entity unites morphological characteristics similar to the large-cell carcinomas, and immunohistochemical ones close to those of neuroendocrine tumours [26]. In large-cell carcinoma in separate focal zones, a positive showing for TTF-1 is noticed. The results obtained go in favour of the researches made so far.

In Nitadory's study, a diffuse and strong expression of CK 7 and CK 18 in large-cell carcinoma is proved [27]. In the study by Pomplun et al. for differentiation between thymic and lung carcinomas, TTF-1 positivity is noticed in 3/10 cases with large-cell undifferentiated lung carcinoma, and negativity in all the others (thymic carcinomas and squamous-cell lung carcinomas) [28].

In the studies where immunohistochemistry with different antibody panels was conducted, their presence in the large-cell carcinoma type was diverse. Namely, in some there is expression of CK7+, TTF1+, CK5-, p63-, in others TTF1+ with variable expression of p63, CK5 and CK7, while in the rest, only CK7+ [17].

The carcinoid tumour showed the strongest expression of NSE, in 100% of the cases, which indicates its sensitivity, as well as the fact that the use of other antibody types (synaptophysin, chromogranin A) has a meaningful role in determining the neuroendocrine status of the neoplasm.

In the small-cell type of lung carcinoma in our study, there the presence of CK-7 was noticed in 66% of the cases. Most of the studies show quite a wide range of different results. The results show CK-7 positivity in 80%, 40% and 9% in the samples with SCLC [27].

In the series of studies for this neoplasm type, it is confirmed that TTF1+, p63-, CK5/6- phenotype is in favour of small-cell lung carcinoma [16].

Our results indicate a very strong expression of TTF-1 in 100% of the cases with small-cell carcinoma.

Although factor TTF-1 shows a strong association with SCLC, the examination's results point to its low specificity which, consequently, makes it an uncharacteristic SCLC marker [29]. However, in immunohistochemical practice TTF-1 is useful in small-cell lung carcinoma differentiation in relation to the other non-pulmonal small-cell carcinomas [30], but it also has a role in differentiating poorly differentiated squamous-cell lung carcinomas [31, 32]. The hyperexpression of Beta-cathenin can be considered as a small-cell carcinoma prognostic factor [33].

The detection of TTF-1 is significant in the bioptic samples with a low number of tumour cells, if there is a presence of inflammatory infiltrate in the sample or when there is plenty of necrosis in the tissue [6]. Small-cell lung carcinoma is an enigma in the diagnostics even for experienced pathologists, which often leads to its incorrect classification in the group of non small-cell lung carcinomas [34].

The immunohistochemical method is desirable and necessary in routine practice in

diagnosing lung carcinomas. It is especially applicable in samples with a small content of bioptic material as well as in artificially damaged bioptic material. However, immunohistochemistry should never be conducted without previous histopathological diagnosis, because of the possible variabilities in the presentation of certain antigens as a result of the increasing tumour heterogeneity. More studies are needed to obtain a more complete picture and a complete, high quality immunohistochemical profile for successful differentiation of different lung cancer types.

The use of singular antibody clones does not show meaningful usefulness in lung carcinoma differentiation, primarily because of the serious overlap of the same into different tumour tissues. However, using an appropriate antibody panel as a specific algorithm type, can have a great role in the successful differentiation of different lung carcinoma types. In that case, using immunohistochemistry, as an important branch of molecular pathology, is very practical in setting differential diagnosis of lung neoplasms. It should be used as an additional step in diagnosis, after making an obligatory histomorphological diagnosis. In lung carcinomas the basic algorithm is mostly used for the distinction between primary and metastatic adenocarcinomas, for the classification of poorly differentiated tumors, and also in determinating the neuroendocrine state of certain tumours.

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Резиме

АНТИГЕНСКИ ФЕНОТИП КАЈ БЕЛОДРОБНИ КАРЦИНОМИ: СТАНДАРДЕН СПЕКТАР ВО ДИСТРИБУЦИЈАТА НА THYROID TRANSCRIPTION FACTOR-1, CYTOKERATIN 7, CYTOKERATIN 20, И NEURON SPECIFIC ENOLASE – БАЗИЧНА ИМУНОХИСТОХЕМИСКА СТУДИЈА НА 21 СЛУЧАЈ

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Имунохистохемијата,како таква, може да биде од корист во рутинската патологија со цел да се направи прецизна и точна дијагноза на белодробните неоплазми. Како резултат на тоа, повеќе детални анализи се потребни во оваа област, со цел да се направи широк спектар на единствени комбинации за одредени белодробни неоплазми. Нашата цел беше да примениме антитетелен панел, да го испитаме и да ја потврдиме неговата корист во диференцијалната дијагноза на белодробен карцином. Дваесет и еден случај (биоптичен и оперативен материјал) на дијагностициран белодробен карцином беа опфатени (RTU FLEX Immunoperoxidase system). Беше направена имунохистохемиска анализа користејќи ги Dako моноклоналните антитела (Cytokeratin 7, CK7; Cytokeratin 20, CK20; Neuron specific enolase, NSE, Thyroid transcription factor-1, TTF1 и Leucocyte common antigen, LCA). LCA позитивитет не беше екпресиран во ниту еден од случаите. Повеќето аденокарциноми беа CK7(+) – 83.3% and TTF1(±) – 50%. CK 20 (+) експресијата покажа метастатски пулмонален депозит на аденокарцином во белодробјето. TTF1(+) – 100%, NSE(+) – 100% and CK7(-) – 66.66%, експресија беше најдена во повеќето случаи на SCLC. NSE(+) –100% имаше најголема експресија кај карциноид туморот, додека TTF1(+) експресијата беше највисока кај SCLC. За планоцелуларниот карцином (SqCC),

имуно-боењето беше негативно за овој панел на антитела, освен фокалната и слаба екпресија на NSE – 60%, по што беа направени дополнителни IHC изледувања користејќи го CKHMW антителото, кое воедно покажа највисока експресија. Есенцијалниот панел на антитела кој го потврдивме и препорачуваме за рутинска базична диференцијална дијагноза на пулмоналните неоплазми е: TTF1, CK7, CK20 и NSE. Поради високиот број преклопувања, IHC не треба да биде спроведена засебно, туку интегрирано во комбинација со морфолошката дијагноза.

Клучни зборови: имунохистохемија, пулмонални неоплазми, антигенска дистрибуција, антителен панел.