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# NEW DATA ON HISTOGENESIS AND HISTOLOGICAL STRUCTURE OF LUNG CANCER

**Background.** Lung cancer (LC) is one of the most common malignant neoplasms in **men** around the world, which poses a number of important challenges for scientists. **Aim.** To analyze the histogenesis, features of the histological structure, and growth of LC. **Materials and Methods.** The surgical material of 81 patients with LC was studied. Histological preparations were stained with hematoxylin and eosin (H&E) using the Papanicolaou method. Immunohistochemical reactions with monoclonals (Ki-67, PCNA) were conducted. **Results.** In histological preparations of all LC types (squamous, adenocarcinoma, and small cell), along with solid growth, tumor growth in the alveoli was determined, which started from the basal membrane and grew toward the alveolus center, as evidenced by the morphological features of growth, tumor spread, and development of necrosis in the center. **Conclusion.** In all the studied histological preparations of LC, tumor growth in the alveoli is noted, which is confirmed by structural and cellular signs and the nature of tumor decay in the alveolus center, which corresponds to the general patterns of development of malignant epithelial tumors.

**Keywords:** lung cancer, histological research, immunohistochemical examination, histogenesis, growth in the alveoli.

Lung cancer (LC) is the most deadly cancer in the world. It occupies a leading position in terms of morbidity and mortality [1—5]. Unfortunately, mortality rates remain high within 1 year from the date of LC detection, and in recent years they have increased from 60 to 67% [3, 6—9]. LC is diagnosed in 65—67% of patients in stages III and IV, when a fatal clinical course is already observed and it is impossible to carry out the entire complex of special treatment [3, 5, 6]. The 5-year survival rates are low: 63.5% in stage I, 43.5% in stage II, and 22.9% in stage III [6]. The lowest five-year survival rate (less than 7%) is registered in patients with small cell lung cancer (SCLC) [5].

Oncopulmonologists are certain of the asymptomatic onset and prolongation of LC until the appearance of clinical symptoms that force the patient to seek medical help [3, 6, 8]. These data

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indicate many unresolved issues in the diagnosis and development of LC, which are to be studied.

For an in-depth study of the LC problem, we have specified the morphological aspects of the lung epithelial tissue in normal conditions. The researchers found that among all epithelial cells in the lung, pneumocytes (alveolocytes) of type II (ATII) are characterized by mitotic activity and the shortest time of renewal, that is, they belong to stem cells (SC) [10]. Along with this, the results of special electron microscopic studies by Zagorulko and Askari [11] also confirm that ATIIs are lung SCs. The presence and morphofunctional features of SC in the lung are reported by many independent scientists [11—19].

On the other hand, known literature data indicate a similar structure of the lung root and its peripheral part. That is, bronchiolo-alveolar structures branch out from large bronchi as reported in the monograph by I. Esipova [cited in 8] and the atlas by F. Netter [16]. The established fact is of decisive importance in the study of the onset and development of pathological processes in the lung. The process of LC development becomes more understandable, taking into account the well-known position expressed by I. Esipova [cited in 20]: "The data of morphology and physiology made it possible to come to a consensus that the functional unit of the lung, which responds integrally under various pathological processes, starts from the terminal bronchiole. This definition is approved by the International Nomenclature". This means that the lung structure in the central and peripheral parts is characterized by the presence of terminal bronchioles, in which, as established later, there are SCs directly related to the onset of the LC development.

Experimental studies allowed Kim et al. [cited in 20] to name bronchiolo-alveolar stem cells (BASC) as the progenitor cells of LC. The authors showed that an increase in the number of BASCs correlates with tumor progression in mice; this fact could confirm that the LC development originates from BASC. A large group of scientists working on experimental models presented the transition of the bronchial epithelium to the alveolar one in the form of a visual scheme, in which signs of cell atypia are clearly demonstrated [7, 13, 14, 17]. It is the place of transition of one type of epithelium to another that is the most vulnerable in the development of a pathological process in the pulmonary system, and the cells themselves are SCs characterized by a high growth potential, which can serve as a trigger for reactive and malignant growths.

An objectively significant fact has been established that corresponds to the general biological pattern of development of pathological processes of tumorous and non-tumorous genesis in the locus of the epithelium the least resistant to pathological effects. It is known in medicine as the "Status resistance minimum", which is directly related to the topic of our report.

The structural and morphological complex of lung epithelial cells was also studied in the experiment of the so-called niche. It exhibits hyperexpression of SC proliferative factors and their stimulating effect on neighboring SCs in the form of uncontrolled growth, which is characteristic of precancerous and cancerous processes [14, 17, 21]. It has been established that niches, as a place of transition of bronchial epithelial cells to alveolar epithelium, are located throughout the lung tissue [22]. This is evidenced by the results of experimental lung carcinogenesis, which showed that regardless of the route of the carcinogen administration (intratracheal or parenteral), cancer, as a rule, develops in peripheral parts of the lung [22].

Many morphological and clinical studies are devoted to the issues of histogenesis and various aspects of LC growth [7, 23—26]. When studying histological preparations of low differentiated LC forms, the authors found areas of double and triple phenotypic differentiation in the composition of tumors, which does not exclude their common histogenesis [12, 26, 27]. These

data allowed scientists to express a maxim about a single origin of LC development, and along with this, to suggest that peripheral LC develops from the epithelium of small bronchi, starting from the distal sections, from bronchioles and, probably, from alveoli (Alv) [28, 29]. Such a probabilistic conclusion indicates the uncertainty of LC histogenesis. The authors also report the development of squamous lung cancer (SqCLC) in the distal parts of the organ [20, 26, 30], which cannot confirm its genesis from the columnar epithelium of the bronchi. The fact that tumorous and non-tumorous processes develop in the bronchiolo-alveolar junctions of the lung is stated by a number of authors [27—29].

It should be noted that in modern cancer pulmonology, the term non-small cell LC (NSCLC), which includes the two most common histological forms — squamous and adenocarcinoma, is accepted. Such a generalized name is due to many common biological, morphological, and clinical characteristics of these LC forms. There is also a similar effectiveness of the treatment of these LC types [4], which indirectly may indicate a single origin of their development.

According to Pennycuick and Janes [2], the complexity of the study of lung carcinogenesis is that already at the early stages of LC development, heterogeneity of cellular mutations is noted. The genetic studies by Gazdar et al. [30] made it possible to state that the three most common aberrations are characteristic of all histological LC types. The data obtained at the genetic level confirm the similarity in the manifestation of the biological essence of SqCLC and adenocarcinoma (AC) and suggest a common origin of their development. Along with this, a number of morphologists came to the conclusion that the cells of the columnar epithelium are the most resistant to any chemical and biological influences, that is, they cannot be the origin of LC development [20].

When studying the synthesis of mucins, the authors proved that MUCI was detected in ATII cells and in elements of the main histological LC types, which makes them more similar in terms of morphofunctional features and can confirm their consistent histogenesis [23].

When clarifying the nature of LC growth, scientists report its proximal-distal spread and growth in the submucosal layer in all layers of the bronchial epithelium [9, 19]. The development of lung AC in the form of a polyp in the pulmonary bulla is known, which confirms the onset and development of AC in the lung parenchyma [29, 31].

A number of scientists have shown that AC is characterized by endobronchial growth. A CT scan revealed a lesion in the form of centrilobular nodules like a "tree with buds", which resembles the pattern of growth of bronchiolo-alveolar structures from large bronchi, as reported in [16] and confirms the multifocal growth of LC.

Summing up the results of various studies concerning the origin and the nature of LC, it can be stated that the data obtained made it possible to rise many questions. However, some studies indicate the uncertainty of LC histogenesis, since many scientists still express their opinion in a hypothetical form, which justifies the need for scientific research to clarify the LC histogenesis and other significant theoretical issues of cancer morphology and clinical practice. Thus, there have been no substantiated answers in the literature to a number of important questions concerning theoretical and clinical data: 1. It remains unclear why LC is the most common and deadly cancer in the world with a mortality rate of up to 1 year from the date of LC diagnosis, extremely low 5-year survival rate and prevalent diagnosis in advanced stages (III—IV). 2. Why do the data on LC histogenesis differ significantly among different researchers? 3. What is the cause to exclude the histogenetic name — bronchioloalveolar LC — from modern international histological classifications [23]?

The aim of the study was to analyze the histogenesis and features of the histological structure and growth of LC.

## Materials and Methods

Surgical material of 81 patients with a diagnosis of LC of clinical stages II and III was investigated. Patients' age ranged from 38 to 72 years but most of them were 50—60 years old (average value of 60.9 ± 1.4 years). The patients were examined and treated at the National Cancer Institute (NCI) of the Ministry of Health of Ukraine. They signed an informed consent on the clinical study of their material for diagnostic and therapeutic purposes. The work was approved by the Ethics Committee of the NCI. The patients did not receive special anticancer treatment before the surgery. The following macroscopic data of the operation material were studied: changes in the mucous membrane of the bronchial tree, the spread of the tumor process, and the features of the morphological structure of LC. Histological preparations were conventionally prepared and stained with H&E as well as by the Papanicolaou method. To determine the proliferative activity of cells, we used monoclonal antibodies against Ki-67 and PCNA (DAKO Cytomation, Denmark). Histological preparations of all patients were carefully studied using an Olympus BX41 microscope at magnifications of ×100, ×200, ×400, and ×1000.

## Results and Discussion

The macroscopic view of the endobronchial and peribronchial parts of the tumor was examined, their ratio was determined. The nature of changes in the bronchial mucosa was studied in all histological LC variants. The macroscopic study of the lung AC growth revealed an unchanged mucous membrane in the material of two patients. It was pale-pink, smooth, and shiny, which testified to its intactness to LC, and around the bronchus and along the length of its outer part, a volumetric growth of a malignant tumor was noted.

There were 45 (55.6%) SqCLC cases, 21 (25.9%) AC cases, and 15 (18.5%) SCLC cases (Table).

Macroscopic examination of the resected material of 81 patients revealed endo-peribronchial LC growth in 61 (75.3%) cases, and in 20 (24.7%) cases the tumor was not associated with the bronchus. A widespread tumor process was revealed in 7 (8.6%) patients. 2 of them showed a circular tumor growth in the bronchi (SqCLC and SCLC). In 2 patients with SqCLC, three bronchi were affected. Exophytic soft growths extended from 1.8 cm to 4 cm along the bronchi length; a large peribronchial part of the tumor was detected. Multiple tumors were found in 3 patients with undifferentiated SCLC.

In various histological LC types, the mucous membrane of the bronchial epithelium was affected independently of the histological LC type. It had the appearance of a softened one; the scrapings from it and the cytological preparations contained cells of SqCLC, AC, or SCLC. In a number of cases, the mucous membrane was significantly thickened, dense, and white, scraping from it was scarce and contained only columnar epithelium cells, that is, the tumor grew under the bronchial epithelium. A similar altered mucous membrane was observed in SCLC and SqCLC.

Staining of histological preparations by two methods, H&E and by Papanicolaou, made it possible to more accurately identify the mesenchymal and epithelial structures. After staining by Papanicolaou, the connective and vascular tissues were stained in green, which made it possible to identify interalveolar septa with the vessels containing erythrocytes. The epithelial tissue of LC was tinted in green-yellow-brown (Figs. 1—3).

*Table.* **General characteristics of the investigated surgical material of patients with lung cancer, n = 81**

| Tumor localization, n (%) | Histological types | | | | | |
|---|---|---|---|---|---|---|
| | SqCLC | | AC | | SCLC | |
| | n | % | n | % | n | % |
| Central, 38 (47) | 24 | 63.2 | 4 | 10.5 | 10 | 26.3 |
| Peripheral, 43 (53) | 21 | 48.9 | 17 | 39.5 | 5 | 11.6 |

When studying the histological structure of LC, the growth of LC in Alv was found in all SqCLC cases, in 86% AC preparations, and 67% cases of SCLC. In addition, growth with solid layers was observed in all phenotypic LC types but prevailed in the structure of SCLC. A peculiarity of the latter is that the growth of the tumor into Alv is solid, that is, cancer cells completely fill the Alv. The presence of clear interalveolar septa evidences that tumor growth occurs in the Alv.

In the histological preparations of AC and SqCLC, a convincing growth of a tumor in the Alv was found, which originated from the basal alveolar membrane and grew into the lumen toward its center (Figs. 2—3). The evidence for such a growth direction is the similarity of the contents in the center of affected Alv and unaffected, that is, preexisting Alv. This content includes (in various proportions) the cells of the first type alveolar epithelium (ATI), macrophages, leukocytes, fine-grained detritus, and, in the presence of a tumor, cancerous cells, their complexes rejected from it (clusters), fragments of cancer cells — "bare" polymorphic nuclei, and fragments of the cytoplasm and necrotic tumor cells. Several morphological features confirm the LC growth from the Alv basal membrane. In particular, when stained with H&E as well as by Papanicolaou, in the basal rows of a tumor that grows from the basal membrane, a more intense staining of the cytoplasm and cell nuclei is noted in the Alv (Figs. 2—3). Superficially growing cells above them have less intensely stained cytoplasm and nuclei. Gradually, toward the center, tumor cells differentiate, become larger and lighter, acquire dystrophic changes, and in the center of the alveolar structures, rejected tumor cells are revealed among the necrotic masses (Figs. 2, 3).

The proof that tumor cells located in the Alv center are part of a solidly growing cancer layer is the observation that one part of the cell is a component of the solid layer, and its other end hangs freely in the lumen of the affected Alv. In addition, cancer cells with characteristic signs of atypia are observed in the Alv center, most often in a state of decay. Upon Papanicolaou staining, tumor cells with intensely stained basophilic greenish cytoplasm or yellowish-brown color contained hyperchromatic nuclei with varying degrees of polymorphy (Fig. 5). The structure of nuclear chromatin is different depending on the histological type of LC. In AC, chromatin is uneven, lumpy, and the nuclei are moderately hyperchromatic. In the case of SqCLC, the nuclei are highly polymorphic, with expressed hyperchromatosis. In some cases, there is a clear polymorphism and hyperchromatosis in dying AC cells. The growth of LC in the Alv demonstrates a well-known regularity in the morphogenesis of epithelial tumors. This means that the tumor grows from the basal membrane as a solid layer, and necrosis develops in its center due to insufficient blood supply, as shown in our histological studies (Figs. 1—3).

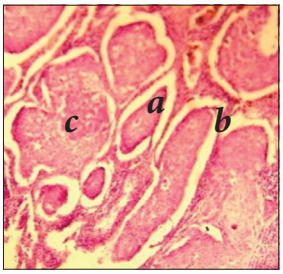
In support of the above, reactions with monoclonal antibodies were carried out. We have found that the cells located on the basal membrane of the Alv have a more intense staining with Ki-67 and PCNA (cell proliferation markers) monoclonals compared to the cells growing superficially above them, that is, more mature, show less intense staining or no staining at all (Figs. 4, 6).

Given the structure of the lung, which has many transitions from the bronchial epithelium to the alveolar (terminal bronchioles), where multipotent SCs are located, we can conclude that all histological LC types have the same onset. SCs have the potential to grow and can play the role of a trigger mechanism for the development of LC [12, 13, 15, 17, 19]. The presence of multiple terminal bronchioles in the lungs explains the wide distribution of LC in the organ parenchyma, which we observed when studying the macroscopic picture of the surgical material as well as other authors [22].

The results of our research and relevant literature data allow us to answer the questions posed in this report.

Lung cancer, the most common and deadly malignant process, develops from ATII cells located in 300—400 million Alvs in the human body. Tumor damage to a part of Alv does not violate the most important function of the lung — the respiratory one, since the human body compensates for it without clinical symptoms, and the patient does not seek timely medical help. The high mortality up to 1 year after the detection and diagnosis of LC is due to the fact that the cancer process affects many Alv, and the removal of a visible and palpable tumor during surgery does not guarantee the absence of affected Alv in the macroscopically unchanged parenchyma of the entire lung. The presence of cancer cells near the tumor, at a distance of 2 cm and 5 cm from the margin of the removed tumor, which we detected by cytological diagnostics in scrapings from incisions of such areas, indicates the possible spread of the tumor in many lung Alv [32]. A possible massive damage of the lung Alv, which may not always manifest itself with clinical symptoms, explains the low 5-year survival of patients after the LC diagnosis and treatment.

An analysis of the literature on LC histogenesis using experimental models over 20 years of the 21st century [23] showed that LC develops from different cells. This situation is not surprising since the initial stage of LC development, when only a small number of alveolar cells is affected, does not cause any clinical symptoms either in experimental settings or in clinical practice. Therefore, it could not be possible to diagnose the initial period of LC growth by morphological, biological, laboratory, or radiological methods. Usually, each researcher considers the LC structure of the minimal volume that can be determined by the X-ray method. However, an already-formed tumor does not allow one to identify the initial cells from which the malignization and tumor growth begin. Each researcher assumes, with the highest probability, some particular origin.



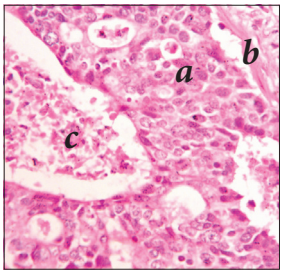
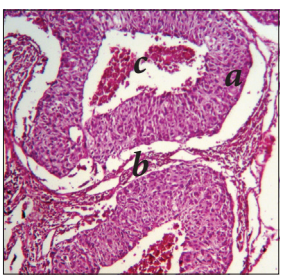




***Fig. 1.*** Histological preparation of LC. H&E staining. ×200. The lung cancer growth in alveoli (***a***), interalveolar septum (***b***), and necrosis in the center of alveolus (***c***)

***Fig. 2.*** Histological preparation of LC, H&E staining. ×1000. The lung cancer growth in alveoli (***a***), interalveolar septum (***b***), necrosis in the center of alveolus (***c***)



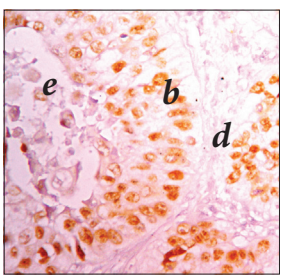
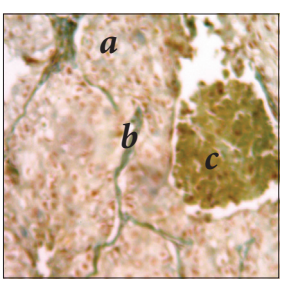




***Fig. 3.*** Histological preparation of LC. H&E staining. ×600. The lung cancer growth in alveoli (***a***), interalveolar septum (***b***), and necrosis in the center of alveolus (***c***)

***Fig. 4.*** Histological preparation of LC.×1000. Immunohistochemistry, monoclonal antibody Ki-67: basal cells (***b***), center of alveolus (***e***), interalveolar septum (***d***)



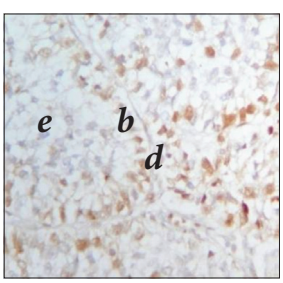




***Fig. 5.*** Histological preparation of LC. Papanicolaou staining. ×1000. The lung cancer growth in alveoli (***a***), interalveolar septum (***b***), and necrosis in the center of alveolus (***c***)

***Fig. 6.*** Histological preparation of LC. ×400. Immunohistochemistry, monoclonal antibody PCNA: basal cells (***b***), center of alveolus (***e***), interalveolar septum (***d***)

In the new International Histological Classifications (WHO) [9, 23], the term bronchioloalveolar LC was excluded and replaced with the so-called lepidic AC. At the same time, the histogenetic name of the type of cancer is excluded. This circumstance indicates that in the literature so far there are no unambiguous data on the histogenesis of LC, which is the subject of this study.

In conclusion, studying the process of histogenesis of LC in the Alv, we have established that LC grows from the basal membrane of Alv toward its center, while cancer cells sequentially differentiate from basal to mature, which corresponds to the well-known morphogenesis of malignant epithelial tumors. The latter undergo necrotic changes resulting in the accumulation of necrotic masses and dying cancer cells in the Alv center.

Presently, it has been proven that in all parts of the lung, there are niches with multipotent SC, located in the zones of transition of the bronchial epithelium to the alveolar (in the terminal bronchioles), from which all histological LC types can develop. This is confirmed by the multifocal LC growth in both the central and peripheral parts of the organ, which was observed in our studies.

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## НОВІ ДАНІ ПРО ГІСТОГЕНЕЗ І ГІСТОЛОГІЧНУ СТРУКТУРУ РАКУ ЛЕГЕНІ

**Вступ.** Рак легені (РЛ) є одним із найпоширеніших злоякісних новоутворень у чоловіків у всьому світі, що ставить перед науковцями ряд важливих проблем. **Мета дослідження.** Визначити гістогенез, особливості гістологічної будови та росту РЛ. **Матеріали та методи.** Досліджено операційний матеріал 81 хворого на РЛ. Фарбування гістологічних препаратів проводили гематоксиліном та еозином (H&E) та за методом Папаніколау. Проводили імуногістохімічні реакції з моноклональними антитілами (Ki-67, PCNA). **Результати.** У гістологічних препаратах у всіх випадках РЛ (плоскоклітинний, залозистий і дрібноклітинний) поряд із солідним ростом визначався ріст пухлини в альвеолах, який починався від базальної мембрани і поширювався до центру альвеоли, про що свідчать морфологічні дані, особливості росту, поширення пухлини та розвитку некрозу в центрі альвеоли. **Висновок.** На всіх досліджених гістологічних препаратах РЛ відзначається ріст пухлини в альвеолах, що підтверджується структурними, клітинними ознаками та характером розпаду пухлини в центрі альвеол, що відповідає загальним закономірностям розвитку злоякісних епітеліальних пухлин.

**Ключові слова:** рак легені, гістологічне, імуногістохімічне дослідження, гістогенез, ріст в альвеолах.