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ABSTRACT

of the dissertation for the degree of Doctor of Philosophy

THE IMPORTANCE OF ELECTRONIC MICROSCOPIC STUDIES IN THE DIAGNOSIS AND PROGNOSTİC ASSESMENT OF CERVICAL CANCER

Specialty: 3224.01 – "Oncology"

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GENERAL DESCRIPTION OF THE RESEARCH

Relevanceand degree of completion of the topic. Due to its structural and functional features, the cervix occupies a special place in the reproductive system, plays an important role in ensuring fertilization, uncomplicated pregnancy, and a timely birth[1,2]. Every year, 530,000 new cases of cervical cancer are diagnosed in the world, and 275,000 women die from this disease every year[3].

According to the American Cancer Society, cervical cancer is diagnosed in an average of 13,000 women each year, with 4500 of them resulting in death. 29,225 women diagnosed with cancer in Azerbaijan in 2001-2011, 2285 of them were diagnosed with cervical cancer [4].

It was determined that the risk group for the development of cervical cancer includes women from the lower social strata, having early sexual activity, premature birth, dark-skinned, having multiple sexual partners, and having an irregular sex life.[5].

In recent years, the method of electron microscopy has been used for the early diagnosis of pathologies of a number of organs.This method allows to accurately determine carcinogenesis

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based on ultrastructural changes in cells. The main feature of the method is based on the structural changes of microstructures and organelles located in the cells.Another feature of electron microscopic study is the detection of normal, dysplastic, atypical, and fully malignant cellsin the early stages of the process. Also, this method can more accurately and easily determine the histological gradation of the tumor process (G1-well differentiated, G2-moderately differentiated, G3-poorly differentiated).Based on the histological gradation, it is possible to speculate on the prognosis of the disease in the future.

At the same time, given the increase in the number of unwarranted surgical interventions on the cervix at the reproductive age, the need for new differential diagnostic methods is growing [6][7].

Taking into account the above, the purpose and tasks of the current scientific research are defined as follows:

The object and subject of the research. The research was conducted in 110 background, precancerous diseases, and 220 patients with various stages of cervical cancer examined and treated at the departments of oncology and gynecology of the Azerbaijan Medical University in 2007-2017.

The purpose of the research - complex clinical, instrumental, morpho-functional, and statistical analysis of cervical cancer, as well as optimization of prognostic criteria of the disease on the basis of determination of electron microscopic indicators.

The tasks of the research. To achieve the solution of the issues envisaged in the research work, the following main tasks have been set:

1. Determination of the histogenesis of tumor tissue in cervical epithelial cancers;

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2. Determination of the diagnostic value of the method of electron microscopy in squamous cell carcinoma of the cervix;

3. Evaluation of electron microscopic study in non-keratinizing cervical cancer;

4. Evaluation of ultrastructural indicators in non-differentiated cervical cancer;

5. Determination of ultrastructural indicators of prognostic criteria in cervical adenocarcinomas;

6. Detection of the probability of recurrence as a result of calculating the prognostic score.

Research methods. Transvaginal ultrasound; extended colposcopy; pathohistological examination of smearsfrom ecto- and endocervix;ecto and endocervical curettesandpathomorphological examination of cervical biopsies;electron microscopic examination of ecto and endocervical curettes, and cervical biopsieswere performed on the patients included in the study. The results of the histological examination were evaluated according to the Histological Classification of Cervical Cancer and the CIN system.

Electron microscopic examinations were carried out on 54 cancer patients in the electron microscopic laboratory at the Department of histology, cytology and embryology of AMU.

Main points presented to the defense of the dissertation:

1. Electron microscopic study of benign and malignant cervical cancer is of independent diagnostic value.

2. The histo-cyto-ultratypical characteristics of tumor cells in the background, precancerous and cancerous processes of the cervix were clarified by the complex clinical, morphological, and electron microscopic studies, and histogenetic identification of nosological forms studied on the basis of these features, principles of optimization of diagnostics, and prognosticating have been developed.

3. Histogenetic and diagnostic identification of cervical neoplasms by electron microscopy is considered a promising direction and can be used in oncological and non-oncological hospitals.

4. The presented ultrastructural method allows clarifying the histogenesis and prognosis of cervical tumors, even in the most complex differentiation.

5. Systematization of the set of electron microscopic features allows determining groups and types of cells, structural and functional changes of cells, and variants of tumors at the ultrastructural level.

6. The systematized algorithm helps to determine the response of neoplasms to any therapeutic effect in any type of tumor at the electron microscopic level, the clinical course of the tumor, short-term and long-term consequences, recurrence and metastasis, andprognosis.

Scientific novelty of the research. The scientific novelty of the research is that the importance of clinical, hormonal, cytological, morphological, and electron microscopy methods in the diagnosis of cervical cancer has been studied, as well as diagnostic and prognostic criteria have been determined.Electron microscopic study and the results obtained allow for a more objective diagnosis of cervical neoplasms and correction of treatment results. Electron microscopic study and the results obtained allow for a more objective diagnosis of cervical neoplasms and correction of treatment results.

Based on the electron microscopic diversity of tumor cells in cervical carcinomas, and even taking into account the difference in a bioptats taken from the same patient in different cells, we have systematized the results obtained in the research.This classification allows us to explain the theoretical basis of the general principles of tumor cells. This system explains the ultrastructural organ-tissue-cell specialization during specific electron microscopic differentiation of tumor cells.

Theoretical and practical significance of the work.

Risk factors for invasive cervical cancer have been identified on the basis of the scientific research. Based on this study, it is possible to assess the importance of functional, cytological, hormonal, morphological, and ultrastructural studies in the early diagnosis of invasive cervical cancerand significantly reduce the incidence of cancer.

The research conducted allows revealing the dynamics of ultrastructural changes depending on the severity of the invasive cervical cancer.

The indicators obtained from the study of ultrastructural parameters allow optimizing the prognosis of the disease. The results also allow the inclusion of additional therapy methods and drugs with specific effects in the treatment program to make the treatment of invasive cervical cancer more effective. The results of the work are important for daily gynecologic oncology, morphological research, as well as for the preparation of relevant teaching materials and the teaching process.

Approbation of the work. The initial discussion of the dissertation was held on April 30, 2018, at the joint scientific meeting of the departments of oncology, histology, embryology, and cytology of the Azerbaijan Medical University.On October 30, 2018, it was re-discussed at the scientific seminar of the Dissertation Council FD 03.021 operating under the National Center of Oncology of Azerbaijan Republic Ministry of Health, and on April 23, 2021 at the scientific seminar of the Dissertation Council FD 1.02.

The main provisions of the dissertation were presented and discussed at the XI Congress of Oncologists and Radiologists of the CIS and Eurasia (Kazan, 2020) and the conference "Actual Problems of Biomedicine" (St. Petersburg, 2020).

Application of the work. The results of the research are applied in the practical activities of the gynecology department of the Oncology Clinic of the Azerbaijan Medical University.

Name of the organization where the dissertation was performed: The dissertation was performed at the departments of oncology, histology, embryology and cytology of the Azerbaijan Medical University.

Publications on the topic of the dissertation. There are 12 published scientific works on the topic of the dissertation. Scientific works on the topic were published in both Azerbaijan (6 articles, 1 thesis) and foreign journals (2 articles, 3 theses).

Total volume of the dissertation in characters with an indication of the separate volumes of the structural units. The dissertation contains 175 pages (281.305 characters) consisting of the introduction (12.327 characters), literature review (56.198 characters), chapter on materials and methods of the research (14.905 characters), 4 chapters covering personal research (12.916 + 29.451 + 47.844. + 21.118 characters), conclusions, results, practical recommendations (45.582 characters). The dissertation contains 20 tables, and 31 figures and graphs. The list of references contains 203 sources (12 local, 191 foreign).

MATERIALS AND METHODS OF THE RESEARCH

Contingent of the research. During 2007-2017, 330 patients with background, precancerous diseases, and cancer were examined and treated at the departments of oncology and gynecology of Azerbaijan Medical University (AMU). As an intact group, bioptats taken from the cervix are used in 15 non-cancerous cases.

The research included 110 patients with background and precancerous diseases of the cervix (group I), and 220 patients with different stages of cervical cancer (group II).

Research methods. Transvaginal ultrasound was performed to determine the condition of the internal organs and denying concominant gynecological diseases. «Voluson E6» was used for transvaginal ultrasound.

To determine the condition of the cervix, extended colposcopy was performed with abinocular colposcope of«Kaps» və «Zeiss»to all patients.

The International Colposcopic Classification (Rio de Janeiro, Brazil, 2011) was used for colposcopic imaging.

Pathocytological and pathohistological examinations of materials from endo- and ectocervix of all patientswere performed.The results of the study were evaluated using the Pap method and the Bethesda system.

Pathohistological examination of postoperative materials was studied in the pathomorphology laboratory of the Oncology

Department at the Azerbaijan Medical University.The results of the histological examination were evaluated according to the Histological Classification of Cervical Tumors and the CIN system.

Electron microscopic examinations were performed on 54 cancer patients in the electron microscopic laboratory under the Department of Histology, Cytology and Embryology of AMU.

Following the results of the research, all patients were diagnosed with the latest clinical diagnosis according to the statistical ICD 10 International Classification of Diseases and Problems of Organs Related to Reproductive Health.

Statistical analysis was performed using the methods of variation, discriminant and regression. All calculations were performed in the EXCEL-2010 spreadsheet and SPSS-20 software package program, the results were summarized in tables and diagrams.

CLINICAL MORPHOLOGICAL PARALLELS OF THE BACKGROUND, PRECANCEROUS DISEASES, AND CANCER OF THE CERVIX

Symptoms of cervical cancer occur especially in the late stages of the disease. The most common symptom of cervical cancer which clinically manifested in patients is bloody secretions (157 patients, 71.4±3.0%). In the majority of patients aged 25-45 years (51 patients, 23.2±2.8%) the secretion was in the form of "bloody spots" after menstruation.The second most common clinical symptom in patients with CC (53 patients, 24.1±2.9%) is white spots in the form of "meat juice".

During the examination of the cervix with a mirror,in 168 patients (76.4±2.9%) we revealed exophytic tumors resembling "cauliflower", often covered with dark scabs and bleeding when touched.In 33 patients (15.0 ± 2.4%) the cervix was hard, the mucous membrane was dark red, and there was an immobile endophyte. In the mixed form (3 patients, 1.4 ± 0.8%), infiltration of the cervical wall was observed along with the exophytic form.Although the cancer was located in the cervical canal (12 patients, 5.5 ± 2.2%),

there was no change in the exophytic part of the cervix, but bleeding occurred when a mirror was inserted into the cervical canal.

A large group of patients (154 patients 70 ± 3.1%) complain of the prolonged menstrual cycle (usually 10-12 days), bloody-purulent drainage. In one group of patients (14 patients 6,4 ± 1.6%) bleeding began 2-10 years after menopause, and in 25 patients (11.4 ± 2.1%) the menopausal age was 40-42.

In patients with cervical cancer in the gynecological history, infertility was found in 19 patients (8.6 ± 1.9%) and spontaneous abortions in 52 patients (23.6 ± 2.9%). Menarche occurred between the ages of 11-15, menopause between the ages of 40-50.

Colposcopy revealed cervical deformity, posterior arch fusion (71 patients 32.3 ± 3.1%), erosive bleeding areas of the mucous membrane (64 patients 29.1 ± 3.1%).

Risk factors for CC include background diseases of the cervix (15.0%), infertility (8.6%), spontaneous abortions (23.6%), menstrual irregularities (70.0%), papilloma virus-16 (57.3%), CIN (23.6%).

LIGHT MICROSCOPIC STUDY OF THE CERVICAL EPITHELIUM DURING BENIGN AND MALIGNANT PROCESSES

Our study found that cervical cancers vary in their rate of development, cytological and histological structures, invasive dissimilation, propensity to metastasize, and sensitivity to chemotherapy.

During our research, light microscopic study of the intact (normal) cervical epithelium was performed in bioptatstaken from macroscopic intact areas in surgical materials.

Light microscopic study of the epithelium during cervical erosion and pseudoerosions. Problems of diagnosis and treatment of benign diseases of the cervix continue to be one of the most pressing problems in our country in terms of their classification and clinical evaluation.These problems lead to a number of difficulties, often unnecessary radicalism and the involvement of patients in long-term conservative treatment. As a result, in some cases, not only the process progresses, but also we witness the recurrence of the disease.

Light microscopic study of the cervical epithelium in intraepithelial neoplasias. Cervical intraepithelial neoplasias (CIN) are precancerous processes and are of great diagnostic importance. Intraepithelial neoplasias are characterized by the presence of dyskaryosis in cervical smears on light microscopy. So that, we found 3 degrees of dyskaryosis (mild, moderate, severe) in cervical epithelial cells based on changes in the nuclear-cytoplasmic ratio and other structural changes (changes in the shape of the nucleolus, location and quantity disorders of chromatin)

Our study found that dyskaryosis signs of CIN I were detected in approximately 20% of cells and CIN II in 20-40% of cells. Symptoms of dyskaryosis were found in approximately 70% of cells in the basal and parabasal layers in CIN III cytograms. CIN II is characterized by numerous basal and parabasal cells.Approximately 50% of cells show symptoms of dyskariosis. In severe intraepithelial lesion (CIN III), altered epithelial cells and lymphoid infiltration are noted. (fig. 1).

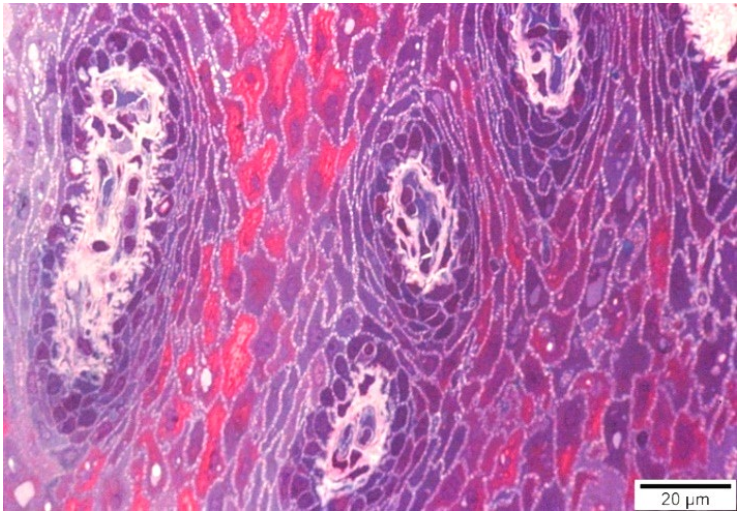

Figure 1.Half thin cut. CIN III.
Die: Methylene blue, Azure-II, Basic Fuchsin.

We used cytological, histological, histochemical and electron microscopic methods used in our study to identify specific morphological features in tumor cells. Changes in the contour and shape of tumor cells, hyperchromia of the nuclear, hypertrophy of the nuclei were noted as the main signs. One of the main signs is a change in the nuclear-cytoplasmic ratio in cell nuclei.

There are 2 types of malignant neoplasms based on the location of the tumor in the cervix. Squamous cell cancer is found in the uterine cervix, and glandular cell cancer is found in the cervical canal.It should be noted that the cancer of glandular cell (adenocarcinoma) can also grow in the background of glandular erosions in the uterine cervix. It is also possible to find foci of squamous cell carcinoma in the cervical canal infected fromthe cervical epithelium.

Cytologically, there are mature (keratinizing variant), moderately mature (non-keratinizing variant) and immature (undifferentiated variant) forms of squamous epithelial origin cancers.

Keratinizing cervical squamous cell carcinoma. In our research, keratinizing cervical squamous cell carcinoma was recorded in 80 patients (36.36±3.2%). Cytologically, it is characterized by atypical squamous, polymorphic plates. Vertical anisomorphism is preserved in these plates, and signs of keratinizing cells are recorded.Keratinizing is mainly distinguished in the central part of the plates and is characterized by the formation of cancerous "pearls". Many glycogens are found in keratinizing squamous cell carcinomas. Severe diversity of atypical epithelial cells is noted in cytologically marked pathologies.

Non-keratinizingcervical squamous cell carcinoma. In our research, non-keratinizing cervical squamous cell carcinoma was recorded in 85 patients (38.63±3.3%). Although the tumor mass is located in the form of individual islets, and the vertical anisomorphism is found to be weak, no signs of keratinizing are generally detected. In the periphery of the plaques of tumor cells, prismatic cells are found, which also correspond to the basal layer of the multilayered squamous epithelium.

Morpho-functional features of adenocarcinomas of cervical canal. In our research, this variant of cervical neoplasms was recorded in 25 patients (11.36 ± 2.1%).Cytologically marked tumors

are classified based on both histological gradation and morphological degree of differentiation.We mainly divided adenocarcinomas into solid, glandular-mucous, mucous, diffuse variants.

In general, adenocarcinomas are cytologically characterized by lysed elements, cell detritus, "naked" nuclei, destroyed in the background of numerous erythrocytes, leukocytes and other inflammatory cells. The main features of this background are acute cell polymorphism, nuclear atypia, changes in the nuclear-cytoplasmic ratio, rough chromatin structures, cells with numerous large nucleoli.In some areas, a small number of giant multinucleated cells, mitotic activity, signs of phagocytosis are also identified.

Various types of cervical cancer. We also often metcytologically scattered cancer cells. Scattered cells are prismatic in shape, the nuclei are large, round and oval, mostly eccentric. The staining intensity of the nuclei varies.

In solid adenocarcinomas closely located, small, low differentiated tumor cells in the smears were found in 3 patients (12±2.2%). They were distinguished by hyperchromic colors, oval and round shapes.The nuclei are relatively large, and have a small, homogeneous chromatin. The amount of cytoplasm in the cells is small, the ratio of nuclear-cytoplasm has changed dramatically (1:3, 1:5).

In glandular mucinous adenocarcinomas (4 ± 1.3%), hyper-chromicstained degenerative, elongated tumor cells with indistinct borders in smears were recorded in 1 patient. The nuclei are large, the chromatin is brittle.

Diffuse cervical cancer is characterized by dense, oval, identical, small cells in 3 patients (12 ± 2,2%). The cytoplasm is small, the nuclei are hyperchromic. Histologically, glandular cancers differ in their histological structures, and degree of differentiation.

Glandular squamous cell carcinoma was observed in 5 patients (20 ± 2,7%). In these types of cancers, undifferentiated in the field of vision, interconnected glandular and squamous structures are found. Fociof multilayered squamous epithelium consist of large, plate-like structures, that can be placed on top of each other, keratinizationre-minds of scales.Glycogen supplements are found in the cytoplasm of

these cells.

Mesonephroid adenocarcinoma of II-type glandular cancer was recorded in 13 patients (52 ± 3.4%). These types of neoplasms are composed of papillae and solid plaques. The tumor cell is light in color as if the cytoplasm is not stained or empty. Glycogen supplementation is recorded in the cytoplasm of cells, and the cells themselves resemble large nuclei, the "head of tacks", based on the annular structure of the cytoplasm. According to us and other authors, the development of mesonephroid adenocarcinomas may be associated with the flowing epithelium.

ELECTRON MICROSCOPIC STUDY DURING BENIGN AND MALIGNANT PROCESSES OF CERVICAL EPITHELIUM

Currently, the application of electron microscopy in the initial diagnosis of tumors is relevant.

Based on the electron microscopic properties of the new derivatives, we divided the tumor cells into 2 groups.

I group tumor cells have ultrastructural organ, tissue and cytospecific characteristics. This group of tumor cells is considered by us to be conditionally differentiated tumor cells.Thus, in the cells we have mentioned, it is possible to identify the ultrastructural features that we encounter in mature cells.

II group tumor cells have no organ-tissue-cytospecific features. Such cells are perceived by us as conditionally undifferentiated tumor cells. Their detection is not of differential diagnostic value, but detection of their value and ultrastructural properties are a very important feature in the differentiation of tumors.

Our research found that the ratio of I group and II group cells varies. This ratio is characterized not only by the same tumor mass, but also by different indicators in different types of tumors (eg, keratinizing and non-keratinizing carcinomas) with the same group.According to this set of signs, in our research we identified 4 variants of the tumor process:

I variant - mainly I group tumor cells predominate;

II variant – II group tumor cells predominate;

III variant – only II group tumor cells are detected;

IV variant – I group and II group tumor cells are found in almost the same amount.

Electron microscopic study of the epithelium during cervical erosion and pseudoerosions. In our study, morphological changes (cytological and histological) during erosion and pseudoerosions in cervical epithelial cells were compared with electron microscopic study, which is a more modern and accurate method.

The first electron microscopic feature that is ultrastructurally visible was vacuolation in the cytoplasm of squamous epithelial cells. In these cells, swelling of the nuclei and stagnation in the karyoplasm were noticeable. Most cells were not only swollen but also had irregular borders. In nuclei, chromatin shifted to karyolemma. In addition to destructive changes, the detection of signs of lysis, pyknosis, rexus indicates the destruction of a number of cells. Electron microscopic changes cover most of the epithelial plaque. There are also very few cells in the surface layer that retain their normal structure. Vertical anisomorphism and stratification are not observed in the lower epithelial cells. The cytoplasm of the cells is in the form of a thin ring. The number of mitotic dividing cells increased dramatically (Fig. 2).

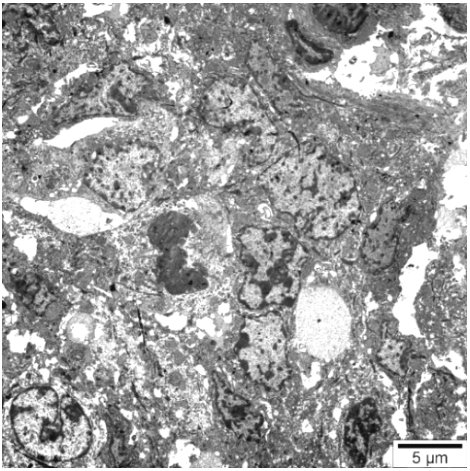

Figure 2. CIN III.Die. Uranyl acetate and lead citrate.

Keratinizing cervical squamous cell carcinoma. Electron microscopically, in the case of keratinizing squamous cell carcinoma of the cervix, we divided the cells ultrastructurally into 2 groups. I group tumor cells have ultrastructural organ-tissue and cytospecific differentiation features. II group includes tumor cells with unclear ultrastructural features. The cell membrane retaines its three-layered structure. Intercellular connections are almost preserved in I group cells, there are many desmosomes, tonofibrils are clearly distinguished, keratohyalin granulesare identified. The amount of desmosomes and tonofibrils is small in II group cells. Chromatin is diffuse in I group atypical cells and condensed in II group cells.

Summarizing the above signs, we have compiled an electron microscopic classification of tumor cells in keratinizing cervical squamous cell carcinomas.

Non-keratinizing cervical squamous cell carcinoma. Electron microscopically we have revealed ultrastructural dystrophic and degenerative changes in the epithelial cells of the cervical mucus during non-keratinizing squamous cell carcinomas (40 patients). The nuclear membrane of basal layer epithelial cells is fragile. The nuclear matrix has a low electron density. Shallow invagination is observed in the nuclear membrane.Most of the nuclear chromatin is condensed, and chromatin masses accumulate around the nuclear membrane. Perinuclear spaces are sharply and unevenly enlarged. Acutely swollen mitochondria are recorded in the perinuclear area of the cytoplasm.

Undifferentiated cervical carsinomas. Electron microscopically, in undifferentiated carcinomas (2 patients), the first sign wefound in epithelial layer cells was numerous electron-dense glycogen supplements located in the cell cytoplasm. Parallel tonofibrils are found in the peripheral division of epitheliocytes. Tonofibrils are characterized by incorrect, irregular placement. Condensed chromatin is located in the nuclei of epitheliocytes.

Morpho-functional features of adenocarcinomas ofcervical canal. In our electron microscopic study, we found dedifferentiated cells in cervical adenocarcinomas and identified their ultrastructural

changes. The main mechanism during the malignancy process is based on the concept of cell dedifferentiation.

Electron microscopic study of cervical adenocarcinomas allows detecting histogenesis and heterogeneity of cells.The research allows us to draw the following conclusions:

1. Adenocarcinomas develop mostly from cambial cells. These cells are to some extent determined and specialized at the organ-tissue level.

2. Adenocarcinoma cells have a specific, ultrastructural differentiation. Also, because of their differentiation orientation, ie their morphogenetic potential, cambial cells specialize in the glandular origin.

3. Summarizing the above symptoms, we have compiled an electron microscopic classification of neoplastic cells in 13 patients with cervical adenocarcinomas.

The results of electron microscopic study. Our comparative analysis of light-microscopic and electron microscopic features during tumor differentiation reveals that as the degree of histological differentiation increases (G1 -> G3), the number of II group tumor cells increases.However, this regularity is not absolute, as in some cases the correspondence between the histological and ultrastructural structure and the degree of differentiation is either difficult to determine or a direct proportion is not recorded.

During our research numerous differentiated neoplastic cells were detected in histologically undifferentiated carcinomas. (for example, in well-differentiated, keratinizing cancers).This feature may be the cause of different clinical and biological course of tumors with the same histological structure and degree of differentiation as determined by light microscopy. Given the ultrastructural heterogeneity of undifferentiated tumor cells, the importance of electron microscopic, electron-histochemical, electron-immunohistochemical, and electronic autoradiographic methods in their proliferation and differentiation mechanisms is clear.

I group differentiated tumor cells are composed of elements with one or more specific ultrastructural cytospecific features.Thus,

in cervical adenocarcinomas, along with differentiated epitheliocytes, mucous gland cells are also found. This parameter should be taken into account when systematizing the ultrastructural characteristics of I group tumor cells, as 2 or more homologous cell types can be found in the same tumor mass.The development of intracellular organelles in I group and II group tumor cells is not the same. In squamous cell carcinomas, desmosomes and tonofibrils are less in one group of cells and more in other groups of cells.While one group of cells had more keratohyalin in grams, the other group had no record at all. In our research, we also found tumor cells that did not differ from normal cells in their ultrastructural features.

Taking into account the above-mentioned ultrastructural diversity, we divided the neoplastic cells we found in our research into 3 types:

I type – cells with numerous, well-developed various organelles in the cytoplasm;

II type – cells with a moderate number, moderately developed organelles in the cytoplasm;

III type – cells with few, poorly developed organelles in the cytoplasm.

We decided to systematize the above set of features and give the following classification:

We included in the I group differentiated tumor cells with ultrastructural organ-tissue-cytospecific features of tumors;

We included in the II group undifferentiated tumor cells without ultrastructural organ-tissue-cytospecific features of tumors.

-The ratio between two groups - reflects the degree of maturity of the tumors

-Types of tumor cells indicate the degree of differentiation of tumor tissue

-Tumor variants are related to the degree of deterioration of the tumor mass.

-Ultrastructurally modified cells reflect cataplasia of tumor elements.

During the classification of tumor cells, we took 5 main

indicators: cell groups, cell types, cell kinds, structural and functional changes of cells, tumor variants.

This systematized classification allows clarifying the response of tumors to any therapeutic effect, clinical course of the tumor, recurrence and metastasis of long-term and short-term results, not only in cervical tumors, but in any type of tumors in general. The activity and predominance of II group tumor cells detected during the above systematized algorithm, the ultrastructural changes observed in one or more types of tumor cells, indicate a worse prognosis.

Our research leads us to the conclusion that the morphogenetic potential of tumor cells is neither more nor less than the morphogenetic potential of normal cambial cells. This potential can be fully or incompletely realized at the cellular level, can be expressed at the level of its entire spectrum in cambial cells, or can be detected in very small volumes.Electron microscopically, in tumor cells, objectively plastic cells arise from deterministic, in some sense specialized cambial cells. That is, the neoplastic process does not occur in differentiated cells.

By applying the histogenesis of the tumor and cell heterogeneity in cervical epithelial cancers, we can draw the following conclusions:

1. Cervical carcinomas develope from determined, specialized cambial cells.

2. Tumor cells have specific, morphological and electron microscopic differentiation, morphogenetic potential.

3. Tumor cells have a monoclonal origin.

The study found that if the malignancy process occured at the level of half-column cells, either undifferentiated cells or undifferentiated and differentiated type I tumor cells were detected in the tumor mass.

In keratinizing cervical squamous cell carcinomas, differentiated tumor cells rich in ultrastructural organ tissue and organelles with cytospecific features (60%) predominated. (I variant).

In non-keratinizing cervical squamous cell carcinomas, the amount of organelles was moderate (50%), the activity of 2 undifferentiated groups of tumor cells, ultrastructural cataplasia of

one or more cell types indicates a worse prognosis. (II variant).

In undifferentiated cervical cancers, only undifferentiated tumor cells with ultrastructurally low organelles (30%) were recorded (III variant).

Differentiated and undifferentiated tumor cells were found in cervical adenocarcinomas in equal amounts (IV variant).

Based on the mentioned and obtained concrete results, it is possible to substantiate the importance of electron microscopy in practical activity and theoretical research, diagnosis, differential diagnosis of tumors, differentiation, histogenesis, biological features of neoplastic cells.

PROGNOSTIC ASSESSMENT OF CERVICAL CANCER

We have developed a mathematical model for predicting recurrence in patients with cervical cancer for 1-3 years.Of the 220 patients with cervical cancer, 80 (36.4±3.2%) had keratinizing squamous cell carcinoma, 85 (38.6±3.3%) had non-keratinizing squamous cell carcinoma, 25 (11.4 ± 2.1%) had adenocarcinoma, and 13 (5.9±1.6%) had mesonephroid type.We kept under control 72 of the 220 cancer patients (32.7±3.2%) for 1-3 years, in 59 patients (26.8 ± 3.0%) recurrence was not detected within 3 years, and in 13 patients (5.9±1.6%) recurrence was detected within 1-3 years. When studying the prognostic criteria of recurrence detection,age, anthropometric indicators, duration of the disease, onset of sexual activity, onset of menopause, infertility, miscarriage, concomitant and extragenital diseases, histological variant of cancer, stage, degree of differentiation, lymph node metastasis, HPV infection, electron microscopic data were checked and the following 9 prognostic criteria were selected:

1. Age;
2. Abortion;
3. HPV;
4. Histological variant;
5. Stage;
6. LN metastasis;

7. Distant metastases;
8. Degree of differentiation;
9. Type of tumor cells.

The following prognostic table was compiled based on the incidence in patients with and without recurrence on these indicators (table).

Table

Prognostic table

N	Indicator	Gradation	REC- n=59	REC + n=13	Informa tiveness	C(a)
1	Age	>=45	23	9		57
		< 45	36	4	0.827	-68
2	Abortions in anamnesis	Yes	34	12		47
		No	25	1	1.640	-171
3	HPV	Yes	24	10		64
		No	35	3	1.245	-94
4	Histological varinat	Keratinizing	26	3		-65
		Non-keratinizing	24	4		-28
		Adenocarcinoma	8	3		53
		Undifferentiated	1	3	1.677	261
5	Stage	T_1	24	1		-167
		T_2	22	3		-48
		T_3	5	4		129
		T_4	8	5	2,529	104
6	LN	N_0	58	6		-76
		N_1	1	7	4.773	346
7	Metastasis	M_0	57	5		-92
		M_1	2	8	4.823	290
8	Degree of differentiation	G_1	20	2		-79
		G_2	20	3		-38
		G_3	16	4		13
		G_x	3	4	1.422	180
9	Type of tumor cells	Organelles- rich	10	7		116
		Organelles -moderate	22	5		3
		Organelles -low	27	1	2.401	-178

In the mathematical model, the Wald coefficient was calculated over the frequencies and the prognostic score was calculated for each gradation of each criterion. A positive prognostic score indicates the likelihood of recurrence. To assess the patient's condition, diagnostic points are summed according to each criterion and the overall prognostic coefficient is calculated. The higher the prognostic coefficient, the higher the probability of recurrence in that patient. A negative result indicates a low chance of recurrence.

CONCLUCIONS

1. Cervical carcinomas develop from determined cambial cells. Tumor cells have morphogenetic potential with morphological and electron microscopic differentiation. [1, 2, 8].
2. Differentiated tumor cells rich in organelles (60%) with ultrastructural organ-tissue-specific features predominate in keratinizing cervical squamous cell carcinomas. (I variant) [1, 6, 10].
3. In non-keratinizing cervical squamous cell carcinomas, the amount of organelles is moderate (50%), the activity of 2 undifferentiated groups of tumor cells, ultrastructural cataplasia of one or more cell types, indicate a worse prognosis. (II variant) [1, 6, 10].
4. In undifferentiated cervical cancers, only undifferentiated tumor cells with low organelles (30%) were recorded. (III variant) [1, 6, 10].
5. Differtiated and undifferentiated tumor cells were detected in cervical adenocarcinoms in equal amounts (IV variant). The mentioned elements belong to heterogeneous cells and cause the growth, development and metastasis of tumors. [1, 6, 10].
6. Based on the prognostic score, more recurrence probability were detected in patients over 45 years of age (informativeness-0.821) with more abortions in anamnesis (1.640), HPV-positive (1.145), high stage (2.29), low degree of differentiation (1,422), lymph node and distant organ metastases (4,823), cells with low organelles in electron microscopic study (2,404). [9].

PRACTICAL RECOMMENDATIONS

1. Histogenetic, ultrastructural and diagnostic identification of benign processes of cervix, precancerous changes and cancers by electron microscopy is one of the promising directions, it is widely used in oncological and non-oncological hospitals.
2. Electron microscopic parameters of different types and differentiated cells of the studied nosological forms are systematized, used in the differential diagnosis of cervical cancer and precancerous processes.
3. The presented ultrastructural methods allow clarifying histogenesis and microscopic review of cervical tumors, to determine their prognosis, even in the case of complex differentiation of cervical tumors.
4. The ultrastructural status of cells should be taken into account in the treatment and prognosis of cervical cancer.
5. In the treatment of both benign and malignant tumors of the cervix, along with clinical and biological factors, and factors that contribute to tumor progression, it is important to study the electron microscopic parameters of tumors.It is advisable to take into account these ultrastructural parameters in the early diagnosis and prognosis of the disease.
6. Electron microscopic features of cervical cancer should be taken into account in daily oncology practice and medical education.

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THE LIST OF ABBREVIATIONS AND SYMBOLS

CC- Cervical cancer

CIN- Cervical intraepithelial neoplasia

HPV- Human papillomavirus

LN- lymph nodes

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