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Errors in the diagnosis of intraepithelial lesions and cervical cancer and modern opportunities to improve the quality of primary screening

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ABSTRACT

The high prevalence of precancerous pathologies and cervical cancer indicates their relevance. Cervical cancer ranks fourth among the causes of mortality of women with cancer worldwide and second in women aged 15–44 years. According to the World Health Organization, approximately 500 thousand new cases of cervical cancer are diagnosed annually worldwide. In Russia, more than 15 thousand new cases are registered annually, and nearly half of them (47.8%) end in death. The increase in the frequency of advanced stages and the increase in mortality among women of reproductive age are of particular concern. According to statistical data from the oncology database of the Moscow Hertzen Cancer Research Institute, the incidence of cervical cancer over 10 years increased by 2.12% annually.

This article presents the results of the statistical analysis of data for assessing the incidence of precancer pathologies and cervical cancer and discusses trends in the spread and juvenation of this pathology as well as its causes. The results of the analysis of errors in diagnosing intraepithelial lesions and modern possibilities for its optimization are also presented.

Keywords: cervical cancer (CC); intraepithelial lesions of the cervix; primary screening; oncocytology; risk factors; colposcopy; fluorescence microscopy; fluorescent and phase-contrast microscopy of smears; confocal microscopy; tumor markers; optical coherence tomography.

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Ошибки в диагностике интраэпителиальных поражений и рака шейки матки и современные возможности улучшения качества первичного скрининга

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АННОТАЦИЯ

Высокая частота распространённости предраковой патологии и рака шейки матки свидетельствует об актуальности данной проблемы. Рак шейки матки занимает 4-е место в структуре смертности женщин в мире от рака и 2-е место в когорте от 15 до 44 лет. По данным ВОЗ ежегодно в мире диагностируется около 500 тыс. новых случаев рака шейки матки; в России ежегодно регистрируется более 15 тыс. новых случаев, из них почти половина (47,8%) заканчиваются летальным исходом. Особую настороженность вызывает увеличение частоты запущенных стадий и рост смертности среди женщин репродуктивного возраста. Согласно статистическим данным базы данных по онкологии МНИОИ им. П.А. Герцена, отмечается прирост заболеваемости раком шейки матки в динамике за 10 лет (с 2007 по 2017 г.), с ежегодным приростом в 2,12%.

В статье приведены результаты обработки статистических данных оценки состояния частоты заболеваемости предраком и раком шейки матки, обсуждаются тенденции к распространению и омоложению данной патологии, а также их причины; дан анализ ошибок в диагностике интраэпителиальных поражений и современные возможности её оптимизации.

Ключевые слова: рак шейки матки (РШМ); интраэпителиальные поражения шейки матки; первичный скрининг; онкоцитология; факторы риска; кольпоскопия; флуоресцентная микроскопия; люминесцентная и фазово-контрастная микроскопия мазков; конфокальная микроскопия; онкомаркеры; оптическая когерентная томография.

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ЭКО•ВЕКТОР

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Cervical cancer (CC) is one of the most prevalent cancers in women, causing over 250,000 deaths annually worldwide [1–7]. In the Russian Federation, CC is the second most common malignant neoplasm in women aged <45 years and the leading cause of death, with an average decrease in life expectancy of 26 years for affected women. In 2017, the Russian Federation registered 17,587 new cases of CC. Every year, 6,000 or more women in Russia die of this disease, with 6,480 deaths recorded in 2017. The incidence of CC has been steadily increasing, with a 23.7% increase over the past decade (2007–2017) [1, 2–7].

The highest incidence rates for CC were observed in the group aged 45–69 years, affecting 27–29 per 100,000 women. For uterine body cancer, the highest incidence rates were observed in the group aged 65–69 years, affecting 67 per 100,000 women. For ovarian cancer, the highest incidence rates were observed in the group aged 65–74 years, affecting 35–37 per 100,000 women. Analysis of age-specific incidence curves in Russia from 1990 to 2005 revealed a tendency toward a decrease in the incidence of CC, and an increase in the incidence of uterine corpus cancer in older age groups. A slight increase in the incidence of ovarian cancer was noted in all age groups [1, 2–7].

The average age of individuals who have died from CC is 60 years. In 2005, the rate of CC-related mortality in Russia was, on average, two times lower than the incidence rate. CC has become the leading cause of death from malignant neoplasms among women aged 20–40 years (15.9%), and ranks fifth among women aged 40–54 years (8.5%) [1, 2–7].

Although CC is currently considered a preventable pathology, it ranks second among all gynecological cancers in the oncological morbidity structure of Russia and shows no tendency to decrease [8]. In Russia, over 15,000 CC cases are registered annually, with 47.8% (>6,000 cases) resulting in fatalities [8]. This is likely due to insufficient oncological caution, underestimation of the clinical situation, diagnostic errors, patient mismanagement, and delayed diagnosis. This increase is concerning because of the higher frequency of advanced stages and mortality among women of reproductive age. Statistical data from the oncology database of the P.A. Gertsen Oncology Institute have shown an increase in the incidence of CC over the past decade, with an annual increase of 2.12% [7, 9–11].

Over the past 10–15 years, the incidence of CC among women of reproductive age has more than doubled on average. This figure is significantly higher in some regions because this increase in pathology is multifaceted and debatable. The following analysis examines these reasons [7, 12, 13].

In developed countries, the incidence of squamous cell carcinoma has slightly decreased in recent years, whereas the incidence of cervical adenocarcinoma has increased. CC is considered a relatively young gynecologic tumor, with the peak incidence occurring at the age of 35 years. Notably, CC cases have been increasing in individuals aged <29 years, with an annual increase of 7%. This statement indicates the lack of health education among the population and inadequate attention to the treatment of background and precancerous cervical diseases in risk groups. In addition, incorrect or unjustified wait-and-see tactics are often used for treating HPV-associated cervical intraepithelial lesions. When examining young women, gynecologists in the general medical network are often unaware of cancer. The increasing number of patients in this age group is believed to reflect the low level of sexual education in the population, which results in inadequate knowledge about the role of contraceptives in preventing sexually transmitted infections (STIs).

In this study, the incidence of cancer, prevalence of the human papillomavirus (HPV) infection, and incidence of CC in women of reproductive age in the Orel region from 2015 to 2022 were analyzed. In 2020, 1,825 cases (51.8%) were registered among the female population in the Orel region, which is equivalent to 449.8 cases per 100,000 women (532.35 in 2019 and 484.95 in 2018 per 100,000 women). Compared with the data from 2018, the incidence decreased by 7.2% in the female population.

In 2020, breast cancer was the most common cancer among women in the Orel region, accounting for 22.2% of all cases. This is an increase from 11.6% in 2019 and 11.1% in 2018. Colon cancer accounted for 7.4% of cases in 2020, a decrease from 8.2% in 2019 and 8.7% in 2018. CC accounted for 4.7% of cases in 2020, a decrease from 5% in 2019 and 5.5% in 2018. Stomach cancer accounted for 5% of cases in 2020, a decrease from 5.5% in 2019 and 5.7% in 2018. Rectal cancer accounted for 4.5% of cases in 2020, a decrease from 6.1% in 2019 and 5.1% in 2018. In addition, 94 new CC cases were detected for the first time in 2021 in the Oryol region. Of these cases, 43.6% were detected in the first stage of the disease, 18.1% in the second, 28.7% in the third, and 9.6% in the fourth. In 2022, 32 cases of advanced CC were detected in the region, including 8 (25%) cases of adenocarcinoma and 24 (75%) of squamous cell cancer [14]. Figure 1 shows the incidence of CC in the Orel region. Neglected cases of CC were analyzed because of the high incidence and mortality rates in the region.

In recent years, the management of patients with various cervical diseases has undergone significant changes because of the increased number of women with HPV infection, higher incidence of inflammatory diseases in the lower genital tract, and disruption of the vaginal microbiota, which plays a crucial role in the development of malignant epithelial transformation. The introduction of new diagnostic and treatment methods in science and practice has improved our understanding of the mechanisms of malignant epithelial transformation. This has enabled the early diagnosis and treatment of patients without unjustified aggressive measures [14–16].

The Orel region has a lower frequency of early detection of malignant neoplasms than the average Russian indicator. CC cases were mainly detected in the third and fourth stages, which can be attributed to both objective and subjective reasons. Over the past decade, this indicator has steadily

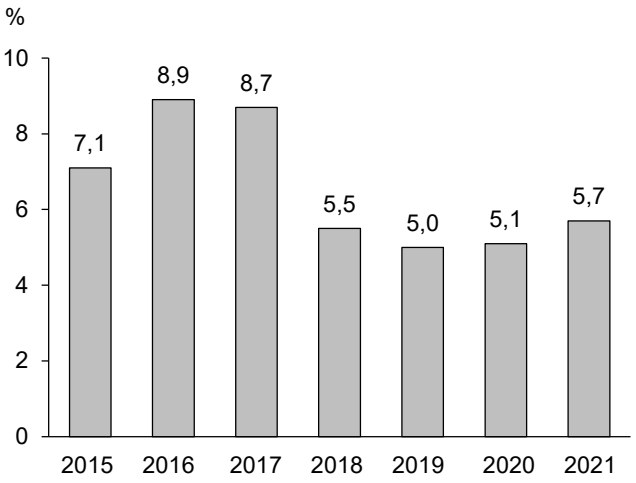

Fig. 1. The incidence of cervical cancer in the Orel region.

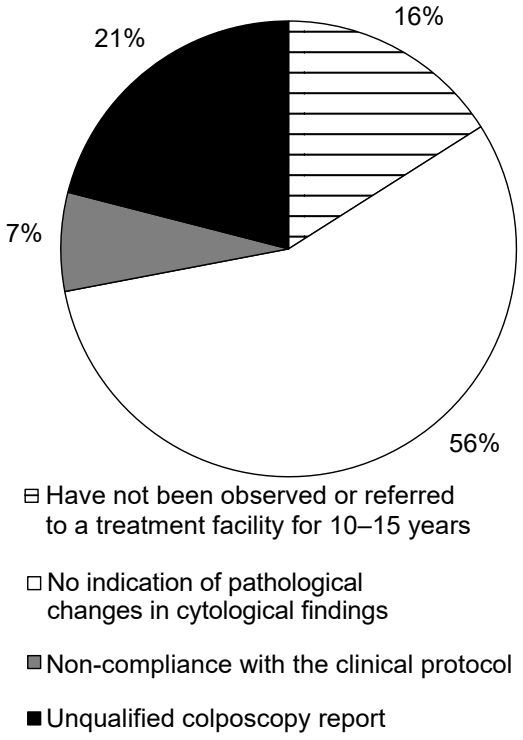

Fig. 2. The reasons for the increase in cancer incidence and late diagnosis of cervical cancer in the Orel region.

increased from 42.9% in 2009 to 53.5% in 2019. In 2020, the rate of early detection of malignant neoplasms decreased slightly because of additional medical examinations conducted over several months [6]. The increase in CC incidence can also be attributed to a sharp rise in the number of cervical precancerous lesions from 2015 to 2019, with vulval intraepithelial neoplasia (VIN) II and VIN III (moderate and severe) being the most common types.

The analysis of the increase in cancer incidence in the region, particularly CC, revealed the following data (Fig. 2):

- Women (16%) with advanced forms of CC had not visited a medical institution for 10–15 years.
- In 56% of women, no pathological changes were detected in cytological reports in the last 3 years.
- In 7% of cases, the clinical protocol was not followed.
- In 21% of cases, the colposcopy report was unqualified, leading to an underestimation of the severity of the lesion.

Risk factors for cervical cancer:

- Early menarche (before the age of 12)
- Early onset of sexual activity (before the age of 16)
- Having several sexual partners
- Frequent changes of sexual partners
- History of STIs (particularly papillomavirus or herpes [HPV-2] in a woman or sexual partner)
- Immunodeficiency
- Smoking (active or passive)
- Early (aged <20 years) or late (aged >45 years) childbirth
- Early menopause (age 45)
- History of multiple abortions
- Background cervical diseases in history
- Inadequate nutrition (deficiency of vitamins A and E and folic acid)
- Occupational hazards (mining, oil refining, coal, and tobacco industries) [14–16].

SCREENING

Screening programs for this population allow for detecting diseases at the precancerous stage or in the initial form of cancer. Accurate diagnosis is crucial in the correct execution of diagnostic procedures. In mass population surveys, cytologic examination of smears from the cervix and cervical canal is considered the leading diagnostic screening test, which allows for the detection of pathological changes in the cervix of women of any age group. The Papanicolaou diagnostic method is widely used internationally. In Russia, a modified version of this method is used, which involves staining smears with hematoxylin and eosin. The material for the cytological study is obtained from the transitional epithelium zone, which contains both the superficial and deep layer cells. Before swabbing, the cervix should be wiped with absorbent cotton. Slides should also be degreased. The material is carefully transferred to the glass, ensuring controlled distribution and moderate thickness of the smear. During cytologic examinations, possible errors that may arise at various stages should be considered:

Various authors have reported different levels of informativeness, sensitivity, and specificity for cytologic screening, ranging from 79.2% to 98%, 50% to 87%, and 69% to 90%, respectively. The concordance between cytologic and histologic findings occurs in 52%–86% of cases and with colposcopic findings in 69.2% of cases. The reliability of initial cancer diagnoses is between 60% and 80% [14–17].

False-negative results are one of the primary issues with cytologic screening, which can lead to failures in CC

diagnosis. Research reveals that up to 31% of cervical malignancies may be associated with negative smears in the 3 years before diagnosis. Several factors contribute to false-negative results, as previously noted [17–18].

For the accurate evaluation of cytologic smears, at least 40%–50% of cells should be located separately. However, with current sampling methods, this indicator is at best 20%. False-positive results are infrequent and are usually caused by errors in interpreting the difference between normal physiological images and inflammation onset. Some authors have noted a difficulty in performing cytologic screening in pregnant and postmenopausal women. This is due to pronounced cytosis in pregnant women and epithelial atrophy in postmenopause.

In an analysis of the causes of cytologic examination failures, only 10% were due to interpretation errors, whereas 90% were caused by improper material collection.

Cytologic studies are still the primary laboratory element of screening programs and the most common test in gynecology and gynecologic oncology. However, cytologic examinations are limited by the high degree of subjectivity and labor-intensive analysis. Data interpretation depends on the experience and qualifications of personnel. Therefore, this analysis does not meet the main requirements for an optimal screening test, which include unification of assessment methods and minimization of subjective evaluations. Mass laboratory tests should not be an individual creation of a highly qualified specialist but an understandable and technologically reproducible process [17–19].

When evaluating the qualifications of cytologists, cytological reports should follow the protocol of the generally accepted classification according to the Bethesda system. Adequate material is defined as having at least 40%–50% of separately located cells. Unfortunately, practicing obstetricians and gynecologists commonly receive a report stating the inadequacy of material, with a cytogram lacking features. If the smear is inadequate, the cytologist should not interpret it but should note the reasons for the inadequacy, such as the presence of small cellular material, inflammatory elements, or many blood elements. A recommendation to repeat the smear should also be included. Furthermore, the cellular composition should be described according to the classification.

A common error made by primary care obstetricians and gynecologists is failure to observe the recommended time interval between the initial and repeat cytology. A repeat cytology should be performed no earlier than 3–4 months after the primary smear to avoid obtaining a false-negative result.

Objective reasons for vulval intraepithelial neoplasia hypodiagnosis:

1. The epithelial junctions are displaced with age because of the natural metaplastic process of the transition zone (TZ) moving toward the center and inside of the cervical canal. This results in the formation of partially visible type II or III TZ with hidden neoplasia foci.

2. The neoplastic process may involve endocervical crypts, and they can be a source of microinvasion. Crypt involvement can complicate the diagnosis of epithelial lesions, leading to treatment failure. The depth of VIN crypt involvement did not exceed 5 mm lateral to the canal wall in 94% of patients. However, their location at a depth of up to 4 mm from the ectocervix can cause incomplete excision in the endocervical region, making it incurable.

CC screening should start 3 years after the first sexual intercourse but no later than the age of 21. Screening should be conducted annually for the first 2 years and then every 2–3 years in the case of negative findings. Screening can be discontinued in women after the age of 70 years who have an intact cervix and if three or more consecutive negative cytologic examinations have been reported within the last 10 years [18–20].

The polymerase chain reaction (PCR) method is widely used for HPV typing because of its high diagnostic value and ability to identify HPV types. However, it can lead to significant overdiagnosis because approximately 80% of HPV infections are short-term and resolve spontaneously with the elimination of the virus. Therefore, a positive PCR result for HPV DNA does not necessarily indicate CC development. Because of the insufficiency of current laboratory methods for the early detection of cervical neoplasia, the continuous search for a marker that indicates a pathologic process with high specificity and prognostic significance is crucial. We strongly believe that the determination of the oncoprotein E7 level can serve as such a test. The presence of oncoprotein E7 in cervical samples is considered unambiguous evidence of the beginning of the malignization of epithelial cells that contain an integrated copy of the HPV genome. An advantage of E7 as an oncomarker is that it is not typically produced in tissues. Its origin is solely related to the life cycle of the integrative form of HPV infection. The method is easily reproducible and minimizes subjectivity. The development of this early diagnostic approach for CC is an accomplishment of Russian science [21].

The varieties of cytological examination are fluorescent and phase-contrast microscopy of smears.

Luminescence microscopy

Luminescence microscopy uses the tropism of acridine orange to analyze DNA and RNA. The luminescence range varies from dark green, which indicates normal cells and nuclei, to orange–red, which indicates cancer cells. This method is complex and laborious; therefore, it is seldom used.

Phase-contrast microscopy

This technique uses the phase changes of light waves passing through transparent objects to make them visible under a microscope. In contrast, confocal microscopy allows the visualization of the structural components of cells without staining. Although confocal microscopy is not as widely used as other techniques, it can provide valuable insights [6].

Colposcopy

Colposcopy is a cost-effective and informative method for assessing the cervical and vaginal epithelium. A colposcope is used to examine the vaginal portion of the cervix and vagina, which provides a magnification of 8–40 times with additional illumination.

Advantages and disadvantages of colposcopy

Informativeness of colposcopy: According to J.V. Bohman, the coincidence between colposcopic and cytologic findings was 69.2%, whereas the coincidence between colposcopic and histologic findings was 86.1%. P.S. Rusakevich reported a sensitivity of 87% for background processes of the cervix, 90.6% for precancerous processes, and 93.2% for cancer *in situ*. V.P. Kozachenko found that colposcopy was effective in diagnosing the initial forms of cancer with an accuracy of 78%–88%.

According to E.B. Kokhanevich, colposcopy can exclude biopsy in 98%–99% of patients with benign pathology. Foreign authors reported an 81.2% coincidence of colposcopic findings with histological findings. The sensitivity of colposcopy for benign pathology is 62%; VIN I, 43%; VIN II, 59%; VIN III, 78%; cancer in situ, 56%; and invasive cancer, 63%. Targeted biopsy can increase the diagnostic accuracy of cervical intraepithelial neoplasia by 25% [14].

Colposcopy technique

Currently, several techniques can be employed for colposcopic examination.

1. Simple colposcopy allows the examination of the cervix at a standard magnification of 8–40 times without medications or dyes.

2. Colposcopy through colored filters allows a detailed study of the cervical epithelium and the vascular pattern of the underlying stroma.

3. Extended colposcopy provides a clearer colposcopic picture using various epithelial and vascular tests. The most common technique for extended colposcopy involves treating the cervical mucosa with 3% or 5% acetic acid and Lugol's solution (Schiller's test).

4. Chromocolposcopy is an extended colposcopy with coloring of the vaginal part of the cervix with different dyes, such as methyl violet, toluidine blue, and hematoxylin.

5. Fluorescence colposcopy is an extended colposcopic technique using acridine orange and uranine violet dyes.

6. Colpocervicoscopy is the simultaneous examination of the epithelium of the vaginal portion of the cervix and endocervix using a cervicoscope.

7. Colpomicroscopy refers to the "lifetime histologic evaluation of the epithelium" of the cervix using a colpomicroscope. In colpomicroscopy, the studied site of the cervical mucosa surface is evaluated at a magnification of 160–280 times, which allows the examination of the epithelial cover and subepithelial vessels at a depth of 70 μm.

Fluorescence spectroscopy

Fluorescent markers enhance the luminescence quantum yield when interacting with tumor cells, providing contrasting luminescence between malignant and unchanged tissue areas. Fluorescence analysis can also detect biochemical changes inherent in neoplasia before the emergence of characteristic morphologic abnormalities.

A growing body of literature has analyzed the use of fluorescence spectroscopy for the diagnosis and screening of cervical neoplasia. Specifically, studies have shown that the concentrations of total tissue hemoglobin and arteriovenous tissue oxygen saturation are lower in patients with high-grade squamous intraepithelial lesions (SIL) than in healthy individuals.

Fluorescence spectroscopy has better diagnostic performance in SIL screening than standard technologies. The method has a sensitivity and specificity of 91% and 93% in differentiating VIN II–III, respectively [22–26].

The implementation of this technique, along with human papillomavirus tests, is expected to reduce CC-related mortality by 10%–15%. In addition, the cost of examination may be reduced by decreasing the number of biopsies and unnecessary treatment. Multimodal hyperspectral imaging has a sensitivity of 97% in the diagnosis of cervical neoplasia, compared with 72% for cytologic screening [12, 26].

Optical coherence tomography

the timely diagnosis of malignant neoplasms is crucial for effective prevention, and this can only be achieved through diagnostic methods with a resolution approaching the cellular level (~10 μm). Currently, several diagnostic technologies have such capabilities, including confocal microscopy, nuclear magnetic resonance (magnetic resonance imaging) using a strong magnetic field, and optical coherence tomography (OCT).

Advantages of optical coherence tomography

1) OCT has a resolution of 10–15 μm, which is 10 times higher than that of other imaging methods such as nuclear magnetic resonance, high-frequency ultrasonography, and X-ray tomography. This allows the study of the object at the level of optical tissue architectonics.

2) The tissue information obtained by OCT is lifetime and reflects both its structure and functional state.

3) OCT is noninvasive and does not cause mechanical trauma or tissue damage. It uses radiation in the near-infrared range with a power of approximately 0.3–1 mW on the object.

4) The maximum depth of probing (up to 1.5–2 mm) is adequate for examining the covering tissues that are not accessible through other high-resolution image acquisition methods.

5) Fiber-optic systems can be inserted into the trocar, catheter, or biopsy channel of endoscopes to deliver probing radiation to the tissue. This allows for high-resolution

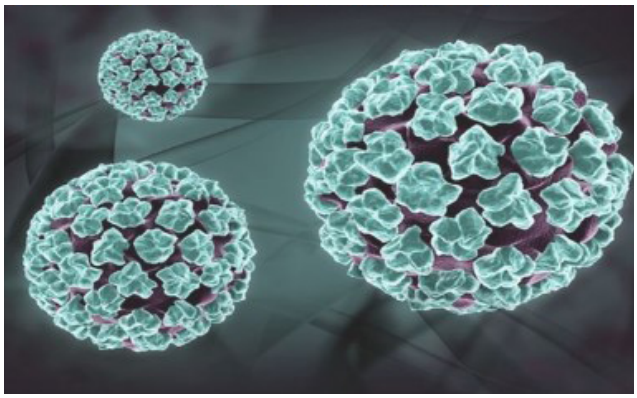

Fig. 3. Human papillomavirus (type 33) by confocal microscopy. (Source: https://ru.qaz.wiki/wiki/Confocal_microscopy)

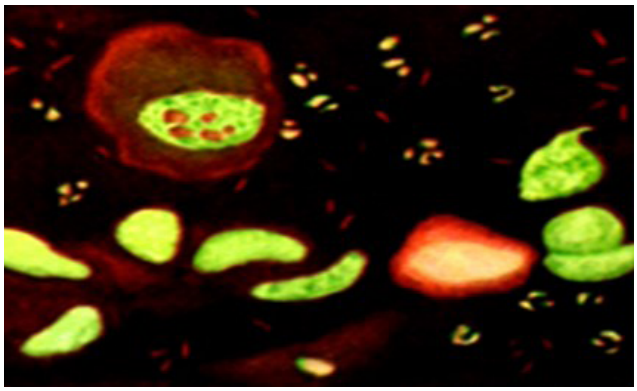

Fig. 4. Cancer cells scraped from the cervix by confocal microscopy. (Source: https://ru.qaz.wiki/wiki/Confocal_microscopy)

imaging of the microstructures of internal hollow or parenchymatous organs.

6) High-speed information acquisition (1.5–2 s) minimizes errors associated with the involuntary movements of the object and the researcher.

7) The device is compact, easy to operate, and relatively inexpensive.

Confocal laser scanning microscopy

Confocal laser scanning microscopy (CLSM) is a foundation for experimental work on living microlevel systems. It allows the acquisition of multidimensional confocal fluorescence images with high resolution and contrast. The term "confocal" refers to the presence of a confocal aperture in the plane optically conjugated to the focal plane of the objective lens. The confocal microscope is distinct from the classical optical microscope because it registers an image of one point of the object at each moment, allowing the recording of a signal from only a thin layer. The full image is then constructed through scanning, which involves either moving the sample or rearranging the optical system.

Recording optical slices in computer memory may allow for the volumetric reconstruction of an object and acquisition of a three-dimensional image. Modern systems allow quick and high-resolution four- and five-dimensional imaging of cell structures, protein localization studies, and tracking of dynamic processes in living cells [24, 27–30].

Advantages of fluorescence microscopy

1) Detection and establishment of the localization and concentration of living and dead microorganisms in cases of colored luminous image of microorganisms on a black background, e.g., *Escherichia coli* (blue means living, red means dead).

2) Possibility of detecting microorganisms in the examined material in small concentrations because of the high degree of image contrast.

3) When using short UV rays, the resolution of the luminescence microscope increases to 0.1 μm, which ensures rapid identification of microbial antigens in the immunofluorescence reaction.

4) Possibility to examine transparent and opaque objects.

5) Possibility of studying life processes in dynamics.

6) Fluorochromes in cytological and histochemical studies, can be diffusely distributed in the cell or selectively stain individual cellular structures or certain chemical compounds of a biological object (Figs. 3 and 4) [27–32].

Confocal microscopy capabilities

Research on CLSM techniques for endoscopic procedures (endomicroscopy) is promising. In the pharmaceutical industry, the manufacturing process of thin-film pharmaceutical dosage forms must be followed to ensure the quality and uniformity of drug distribution. Confocal microscopy is also used to study biofilms, which are complex porous structures that serve as preferred habitats for microorganisms [27–30]. Some temporal and spatial functions of biofilms can only be understood by micro- and mesoscale study of their structure. A microscale study is necessary to reveal the activity and organization of individual microorganisms.

CONCLUSIONS

Implementation of innovative diagnostic methods for cervical intraepithelial lesions, along with HPV testing, can improve the quality of cytological findings by reducing false-positive and false-negative results. This, in turn, can reduce the mortality rate from CC by 10%–15% in the future.

The cost of the examination can be reduced by decreasing the number of biopsies and unnecessary treatments. Multimodal hyperspectral imaging has a sensitivity of 97% in diagnosing cervical neoplasia, compared with 72% for cytologic screening [32–38].

The use of CLSM techniques for endoscopic procedures, such as endomicroscopy, shows promise in providing a non-invasive, lifetime diagnosis of malignant transformation in cases of CC and endometrial cancer.

ADDITIONAL INFO

Authors' contribution. All authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

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Competing interests. The authors declares that there are no obvious and potential conflicts of interest associated with the publication of this article.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Финансирование. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

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