POSSIBILITIES OF FLUORESCENCE DIAGNOSTICS IN DETECTING MULTICENTRIC FOCIES OF CERVICAL DYSPLASIA

Smailova S.B.[1], Shanazarov N.A.[1], Grishacheva T.G.[2], Salmagambetova S.Zh.[1], Aldabergen G.S.[1]
[1]Medical Center Hospital of the President's Affairs Administration of the Republic of Kazakhstan, Astana, Republic of Kazakhstan
[2]First St. Petersburg State Medical University named after Academician I. P. Pavlov, St. Petersburg, Russia

Abstract

Colposcopy allows the examiner to localize potential lesions, assess the severity of the lesion, and obtain a colposcopic guided biopsy. This method has limited sensitivity and specificity, raising serious concerns about the possibility of missing cervical dysplasia. Fluorescent methods for diagnosing precancerous diseases of the cervix and early forms of cancer have an extremely high sensitivity, reaching 90%. The presented results of the study allow us to fully declare the high information content of fluorescent colposcopy in identifying dysplastic lesions on the cervix.

Keywords: cervical dysplasia, fluorescent diagnostics, cervical biopsy, photodynamic therapy.

Contacts: Smailova Sandugash Bakhytbekovna e-mail: Sandugash.smailova@bk.ru

For citation: Smailova S.B., Shanazarov N.A., Grishacheva T.G., Salmagambetova S.Zh., Aldabergen G.S. Possibilities of fluorescence diagnostics in detecting multicentric focies of cervical dysplasia, *Biomedical Photonics*, 2023, vol. 12, no. 3, pp. 11–14. doi: 10.24931/2413–9432–2023–12-3-11–14.

ВОЗМОЖНОСТИ ФЛЮОРЕСЦЕНТНОЙ ДИАГНОСТИКИ В ВЫЯВЛЕНИИ МУЛЬТЦЕНТРИЧНЫХ ОЧАГОВ ДИСПЛАЗИИ ШЕЙКИ МАТКИ

С.Б. Смаилова[1], Н.А. Шаназаров[1], Т.Г. Гришачева[2], С.Ж. Сальмагамбетова[1], Г.С. Алдаберген[1]
[1]РГП Больница Медицинского Центра Управления Делами президента на ПХВ, Астана, Республика Казахстан
[2]Первый Санкт-Петербургский государственный медицинский университет имени академика И. П. Павлова, Санкт-Петербург, Россия

Резюме

Кольпоскопия позволяет исследователю локализовать потенциальные поражения, оценить тяжесть поражения и получить кольпоскопически направленную биопсию. Данный метод имеет ограниченную чувствительность и специфичность, вызывая серьезные опасения по поводу вероятности пропуска дисплазии шейки матки. Флуоресцентные методы диагностики предраковых заболеваний шейки матки и ранних форм рака обладают крайне высокой чувствительностью, достигающей 90%. Представленные результаты исследования позволяют в полной мере заявить о высокой информативности флуоресцентной кольпоскопии в выявлении диспластических очагов на шейке матки.

Ключевые слова: дисплазия шейки матки, флуоресцентная диагностика, биопсия шейки матки, фотодинамическая терапия.

Контакты: Смаилова С.Б., e-mail: Sandugash.smailova@bk.ru

Ссылка для цитирования: Смаилова С.Б., Шаназаров Н.А., Гришачева Т.Г., Сальмагамбетова С.Ж., Алдаберген Г.С. Возможности флюоресцентной диагностики в выявлении мультцентричных очагов дисплазии шейки матки // Biomedical Photonics. – 2023. – Т. 12, № 3. – С. 11–14. doi: 10.24931/2413–9432–2023–12–3-11–14.

Introduction

In 2020, 604127 cases of cervical cancer (CC) and 341831 deaths due to this malignant neoplasm were reported worldwide [1]. CC is the fourth most commonly diagnosed cancer and the fourth leading cause of cancer death in women worldwide [2]. In the Russian Federation in 2021, more than 15 thousand women were diagnosed with this pathology for the first time. Mortality from cervical cancer amounted to more than 6 thousand cases [3].

Screening for precancerous diseases and cervical cancer in target groups of patients in the Republic of Kazakhstan (RK) is carried out using routine cytological examination of the Papanicolaou smear. If an abnormal result is detected, by an algorithm, colposcopy and testing to detect DNA of highly oncogenic types of human papillomavirus (HPV) is performed.

Women aged 30 to 70 years are subject to mandatory cancer screening in the Republic of Kazakhstan once every 4 years. According to the results of the cytological screening method for CC, in 2021, a total of 757454 women aged 30–70 years were examined. Of this number, precancerous diseases were identified in 0.99% (7498), and CC was detected in 0.04% (319). The incidence of cervical cancer (the proportion of newly diagnosed cases) was 1804 women (18.3 per 100 thousand female population versus 17.2 in 2020). The mortality rate from cervical cancer in 2021 has not changed compared to 2020 and amounted to 6.0 per 100 thousand female population [4].

Despite the current existence of clear provisions on precancerous processes and CC, the availability of reliable test control (cytological, colposcopic) of CC remains an urgent problem in gynecological oncology to this day [5].

CC is a visually accessible form of a malignant tumor, so the possibilities for early detection are practically unlimited. For this, timely and correct use of accessible and informative diagnostic methods is sufficient. In addition, timely treatment of precancerous processes of the cervix can prevent the development of cervical cancer [6].

It has been proven that the cause of the development of cervical cancer may be persistent HPV infection in the cervical tissue. Human papillomavirus (HPV) is the most common sexually transmitted infection [7]. With long-term persistence of HPV infection in a woman's body, dysplastic processes occur on the cervix, in the absence of treatment of which the next stage of development will be cervical cancer.

The Pap smear is a screening test, and depending on the abnormality, the next step in evaluating the process is a colposcopy. The procedure involves treating the cervix with a 5% acetic acid solution, followed by examining the integumentary epithelium under magnification. Pathologically altered areas of the cervical mucosa are characterized by persistent whitening of the epithelium. A targeted biopsy taken from these areas is sent for histological examination to determine the nature of the changes. Colposcopy, which is currently included in World Health Organization (WHO) guidelines for women infected with HPV, remains the reference standard for biopsy to confirm precancer and CC [8].

One of the priority areas in modern medicine is the use of fluorescence diagnostics (FD) through the introduction of exogenous photosensitizers (PS). When they enter the bloodstream, PSs most often bind to serum proteins, forming complex compounds [9]. The resulting complexes of PS with proteins are absorbed by endothelial cells in the capillaries of the bloodstream. Then they bind to the adventitia of blood vessels and PS enters the extracellular matrix with subsequent accumulation and retention in pathologically altered cells. When excited by blue light, red fluorescence is generated, resulting in a distinct fluorescent contrast between tumor/pretumor and healthy surrounding tissue [10].

The use of PD methods in the complex diagnosis of precancerous changes in the cervix increases diagnostic efficiency in identifying the location and size of lesions, thus facilitating more complete visualization for subsequent treatment. The main parameter of the reliability of this diagnostic method is histological confirmation of the dysplastic status of fluorescent lesions. At the same time there is a correlation between the degree of tissue dysplasia and fluorescence intensity. Fluorescence imaging can facilitate the detection of extraclinical lesions [11].

Fluorescence diagnosis represents a promising opportunity in the diagnosis of diseases in a wide range of medical disciplines, such as gynecology, dermatology, gastroenterology, surgery, neurosurgery and urology. In gynecology, many studies have been conducted evaluating the utility of fluorescent detection of cervical dysplasia, breast cancer, endometrial diseases, ovarian cancer and endometriosis [12].

A number of studies show that, due to high selectivity for tumors and low toxicity to healthy tissues, diagnostics based on modern PSs are a promising tool for the non-invasive identification of cervical intraepithelial neoplasia [13]. The use of fluorescent colposcopy allows the doctor to adequately assess the size and boundaries of lesions to select PDT parameters [14]. In the present study, we assessed the informativeness of fluorescent colposcopy in identifying cervical dysplasia by histological examination of biopsy specimens from foci of red fluorescence.

Materials and Methods

The study was performed as part of the project for the implementation of the scientific and technical program BR18574160 "Development of innovative technologies that increase the efficiency of diagnosis and treatment

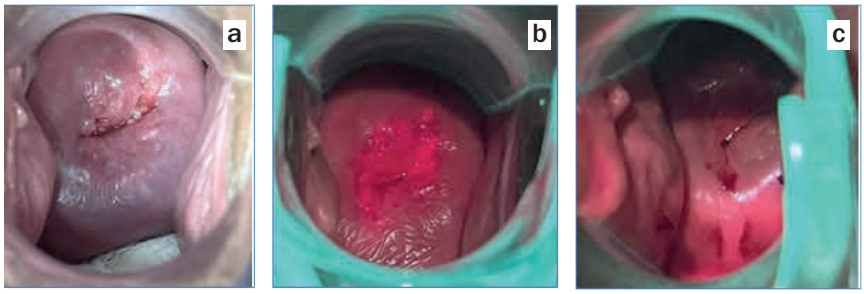

Рис. 1. Кольпоскопическая картина шейки матки пациентки с HSIL и 4 типами ВПЧ: a – в видимом свете после обработки шейки матки 5% раствором уксусной кислотой; b,c – в режиме флуоресцентного обследования.
Fig. 1. Colposcopic image of the cervix of a patient with HSIL and 4 types of HPV: a – in visible light after treating the cervix with a 5% solution of acetic acid; b,c – in fluorescent examination mode.

of background and precancerous diseases of the cervix associated with the human papillomavirus", agreement No. 39-PTsF-23-24 dated January 25, 2023, carried out at the Medical Hospital Center for Administration of Presidential Affairs of the Republic of Kazakhstan, aged 18 to 49 years. The average age was 37.3±4.9 years. A positive result for highly oncogenic types of PCR for HPV and an established cytological diagnosis distributed as follows: LSIL n=38 (95%) and HSIL n=2 (5%), 7 (17.5%) women had previously undergone surgical treatment of the cervix.

The colposcopic examination was performed on a modern device – video colposcope SLV-101 HD with a digital FullHD video camera, with LED lighting, optical zoom up to 23 times and recording of images on a personal computer with an installed program, with a built-in yellow filter for leveling ultraviolet light. A chlorine-type drug was used as a photosensitizer.

Among 40 participants, highly oncogenic HPV types were distributed as follows: type 16 – in 12 (24.5%) patients, type 31 – in 7 (14.3%) patients, type 58 – in 7 (14.3%) patients, type 18 – in 5 (10.2%) patients, type 33 – in 3 (6%) patients, type 35 – in 3 (6%) patients, type 45 – in 3 (6%) patients, type 56 – in 3 (6%) patients, type 59 – in 3 (6%) patients, type 52 – in 2 (4.1%) patients, type 51 – in 1 (2%) patients.

Visual observation of the fluorescence images was possible with the naked eye. For documentation, the video colposcope camera was equipped with additional functions: a yellow filter was built into the eyepiece to improve fluorescence detection and neutralize the violet light of an ultraviolet flashlight. This allowed better targeting of negative fluorescence regions and a clear delineation of positive fluorescence images compared to negative regions by increasing the contrast between red and blue light.

Results

As a result of the study, the following data were obtained: out of 40 patients, fluorescent lesions were histologically verified as dysplasia in 39 (97.5%) women. In one case, fluorescence colposcopy revealed a combined pathology of the genital tract in the patient in the form of morphologically confirmed moderate dysplasia of the vaginal mucosa (the woman was removed from the project for further examination).

The high percentage of recurrence of cervical dysplasia after surgery, in the study in 17.5% of participants, can be explained by underestimation of the prevalence of the process and, as a consequence, non-radical treatment.

Clinical observation

A 34-year-old patient with HSIL and 4 types of HPV underwent colposcopy of the cervix in visible light and fluorescence diagnosis. In Fig. 1a a colposcopic picture after treatment of the cervix with a 5% solution of acetic acid can be seen, where a rough mosaic, open glands with a rough rim of keratinization are clearly visible. At fluorescence colposcopy (Fig. 1 b, c), areas of red fluorescence correspond to areas of aceto-white epithelium, and a bright glow is additionally detected in the posterior fornix and the right lateral wall of the vagina. A biopsy was taken from this area. The histological result is moderate epithelial dysplasia of the vaginal epithelium (VAIN 2). This pathology is usually combined with cervical dysplasia, while it is rare as an independent nosology,.

Conclusion

Fluorescence colposcopy makes it possible to diagnose multifocal lesions on the cervix, in particular pathologies localized outside the cervix, and to correctly assess the boundaries of the lesion, not inferior to colposcopy using the acetic acid test.

REFERENCES

1. Bray F., Ferlay J., Soerjomataram I., Siegel R.L., Torre L.A., Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, *CA Cancer J Clin*, 2018, vol. 68(6), pp. 394-424.
2. Small W., Bacon M.A., Bajaj A., Chuang L.T., Fisher B.J., Harkenrider M.M., et al. Cervical cancer: A global health crisis: Cervical Cancer: A Global Health Crisis, *Cancer*, 2017, vol. 123(13), pp. 2404-2412.

ЛИТЕРАТУРА

1. Bray F., Ferlay J., Soerjomataram I., Siegel R.L., Torre L.A., Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries // CA Cancer J Clin. – 2018. – Vol. 68(6). – P. 394-424.
2. Small W., Bacon M.A., Bajaj A., Chuang L.T., Fisher B.J., Harkenrider M.M., et al. Cervical cancer: A global health crisis: Cervical Cancer: A Global Health Crisis // Cancer. – 2017. – Vol. 123(13). – P. 2404-2412.

3. The Institute of Leadership and Health Care Management of the Federal State Autonomous Educational Institution of Higher Education "The I. M. Sechenov First Moscow State Medical University" (Sechenov University). The condition and tendencies of cervical carcinoma diagnostic in the Russian Federation, *Probl Soc Hyg Public Health Hist Med*, 2021, vol. 29(6).
4. Kaidarova D., Shatkovskaya O., Ongarbayev B., Seisenbayeva G., Azhmagambetova A., Zhylkaidarova A., et al. Indicators of the oncology service of the Republic of Kazakhstan, 2021 (statistical and analytical materials). JSC «kazakh institute of oncology and radiology» at the ministry of the healthcare of the Republic of Kazakhstan, 2022.
5. Holcakova J., Bartosik M., Anton M., Minar L., Hausnerova J., Bednarikova M., et al. New Trends in the Detection of Gynecological Precancerous Lesions and EarlyStage Cancers, *Cancers*, 2021, vol. 13(24), p. 6339.
6. World Health Organization. WHO technical guidance and specifications of medical devices for screening and treatment of precancerous lesions in the prevention of cervical cancer, *Geneva: World Health Organization,* 2020.
7. Graham S.V. The human papillomavirus replication cycle, and its links to cancer progression: a comprehensive review, *Clin Sci*, 2017, vol. 131(17), pp. 2201-2221.
8. Valls J., Baena A., Venegas G., Celis M., González M., Sosa C., et al. Performance of standardised colposcopy to detect cervical precancer and cancer for triage of women testing positive for human papillomavirus: results from the ESTAMPA multicentric screening study, *Lancet Glob Health*, 2023, vol. 11(3), pp. e350-360.
9. Sabban F., Collinet P., Cosson M., Mordon S. Technique d'imagerie par fluorescence: intérêt diagnostique et thérapeutique en gynécologie, *J Gynécologie Obstétrique Biol Reprod*, 2004, vol. 33(8), pp. 734-38.
10. He Z., Wang P., Liang Y., Fu Z., Ye X. Clinically Available Optical Imaging Technologies in Endoscopic Lesion Detection: Current Status and Future Perspective, *J Healthc Eng*, 2021, vol. 2021, pp. 1-27.
11. Collinet P., Delemer M., Jouve E., Regis C., Farine M.O., Vinatier D., et al. Fluorescence diagnosis of cervical squamous intraepithelial lesions: A clinical feasability study, *Photodiagnosis Photodyn Ther*, 2007, vol. 4(2), pp. 112-116.
12. Löning M., Diddens H., Friedrich M., Altgassen C., Diedrich K., Hüttmann G. Fluoreszenzdiagnostik und photodynamische Therapie mit 5-Aminolävulinsäure induziertem Protoporphyrin IX in der Gynäkologie: eine Übersicht, *Zentralblatt Für Gynäkol*, 2006, vol. 128(6), pp. 311-317.
13. Vansevičiūtė R., Venius J., Letautienė S. 5-Aminolevulinic acid-based fluorescence diagnostics of cervical preinvasive changes, *Medicina (Mex)*, 2014, vol. 50(3), pp. 137-143.
14. Hillemanns P., Weingandt H., Baumgartner R., Diebold J., Xiang W., Stepp H. Photodetection of cervical intraepithelial neoplasia using 5-aminolevulinic acidinduced porphyrin fluorescence, *Cancer*, 2000, vol. 88(10), pp. 2275-2282.

3. The Institute of Leadership and Health Care Management of the Federal State Autonomous Educational Institution of Higher Education "The I. M. Sechenov First Moscow State Medical University" (Sechenov University). The condition and tendencies of cervical carcinoma diagnostic in the Russian Federation // Probl Soc Hyg Public Health Hist Med. – 2021. – Vol. 29(6).
4. Kaidarova D., Shatkovskaya O., Ongarbayev B., Seisenbayeva G., Azhmagambetova A., Zhylkaidarova A., et al. Indicators of the oncology service of the Republic of Kazakhstan, 2021 (statistical and analytical materials). JSC «kazakh institute of oncology and radiology» at the ministry of the healthcare of the Republic of Kazakhstan. – 2022.
5. Holcakova J., Bartosik M., Anton M., Minar L., Hausnerova J., Bednarikova M., et al. New Trends in the Detection of Gynecological Precancerous Lesions and EarlyStage Cancers // Cancers. – 2021. – Vol. 13(24). – P. 6339.
6. World Health Organization. WHO technical guidance and specifications of medical devices for screening and treatment of precancerous lesions in the prevention of cervical cancer // Geneva: World Health Organization. – 2020.
7. Graham S.V. The human papillomavirus replication cycle, and its links to cancer progression: a comprehensive review // Clin Sci. – 2017. – Vol. 131(17). – P. 2201-2221.
8. Valls J., Baena A., Venegas G., Celis M., González M., Sosa C., et al. Performance of standardised colposcopy to detect cervical precancer and cancer for triage of women testing positive for human papillomavirus: results from the ESTAMPA multicentric screening study // Lancet Glob Health. – 2023. – Vol. 11(3). – P. e350-360.
9. Sabban F., Collinet P., Cosson M., Mordon S. Technique d'imagerie par fluorescence: intérêt diagnostique et thérapeutique en gynécologie // J Gynécologie Obstétrique Biol Reprod. – 2004. – Vol. 33(8). – P. 734-38.
10. He Z., Wang P., Liang Y., Fu Z., Ye X. Clinically Available Optical Imaging Technologies in Endoscopic Lesion Detection: Current Status and Future Perspective // J Healthc Eng. – 2021. – Vol. 2021. – P. 1-27.
11. Collinet P., Delemer M., Jouve E., Regis C., Farine M.O., Vinatier D., et al. Fluorescence diagnosis of cervical squamous intraepithelial lesions: A clinical feasability study // Photodiagnosis Photodyn Ther. – 2007. – Vol. 4(2). – P. 112-116.
12. Löning M., Diddens H., Friedrich M., Altgassen C., Diedrich K., Hüttmann G. Fluoreszenzdiagnostik und photodynamische Therapie mit 5-Aminolävulinsäure induziertem Protoporphyrin IX in der Gynäkologie: eine Übersicht // Zentralblatt Für Gynäkol. – 2006. – Vol. 128(6). – P. 311-317.
13. Vansevičiūtė R., Venius J., Letautienė S. 5-Aminolevulinic acid-based fluorescence diagnostics of cervical preinvasive changes // Medicina (Mex). – 2014. – Vol. 50(3). – P. 137-143.
14. Hillemanns P., Weingandt H., Baumgartner R., Diebold J., Xiang W., Stepp H. Photodetection of cervical intraepithelial neoplasia using 5-aminolevulinic acidinduced porphyrin fluorescence // Cancer. – 2000. – Vol. 88(10) – P. 2275-2282.