

CERVICAL CANCER

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Abstract. Cervical cancer, or cervical carcinoma, is a malignant disease of the female reproductive system characterized by the transformation of epithelial cells of the cervical canal. According to statistics, approximately 20 females per 100,000 population are affected, and the mortality rate is 9 cases per 100,000 women. Nearly one third of patients present to the physician with advanced stages of the disease. With timely diagnosis and appropriate treatment, complete recovery is achievable.

Keywords: signs of cervical cancer, forms of cervical cancer, causes of cervical cancer; symptoms of cervical cancer; invasive types of cervical cancer.

Cervical cancer develops through several stages:

- Dysplasia of epithelial cells (a precancerous condition).
- Malignant transformation of cells progressing to non-invasive intraepithelial carcinoma.
- Microinvasive stage (often asymptomatic; surrounding tissues may be affected and tumor cells may enter the lymphatic stream).
- Clinical (invasive) stage (symptoms appear; connective tissue and other internal organs are involved; metastases may form).

Cervical cancer typically progresses slowly, and a long-standing dysplastic process usually precedes overt malignancy. When females attend regular preventive gynecological examinations, the disease can be detected at very early stages when minimally invasive treatment is possible and full recovery can be expected. Neglect of preventive visits to a specialist remains a major contributor to mortality from cervical cancer.

Symptoms of Cervical Cancer

Early stages of cervical cancer are usually asymptomatic. Clinical symptoms generally indicate tumor enlargement and spread, involvement of internal organs and the lymphatic system. The most prominent signs of cervical cancer include:

- Heavy menstrual bleeding (menorrhagia);
- Intermenstrual (metrorrhagia) bleeding;
- Contact bleeding (after sexual intercourse, physical exertion, or gynecological examination);
- Postmenopausal bleeding;
- Copious watery, clear, whitish or yellowish vaginal discharge;
- Pelvic pain (in the region of the pubis and coccyx).

In advanced cases, tumor necrosis may produce a foul-smelling discharge described as like 'meaty washings'. When the tumor invades the tissues of the rectum or urinary bladder, fistulas can form and fecal matter or urine may pass into the vagina.

Causes of Cervical Cancer

Human papillomavirus (HPV) infection is recognized as the principal cause of cervical cancer. High-oncogenic-risk HPV types (notably types 16 and 18) are detected in the majority of patients diagnosed with cervical carcinoma. The risk of disease increases in the presence of provoking factors, including:

- Tobacco smoking;
- Sexually transmitted infections;
- Chronic inflammatory diseases of the reproductive organs;
- Cervical erosion;
- Early onset of sexual activity;
- History of induced abortions;
- Multiple childbirths;
- Poor nutrition;
- Deficiency of vitamins A and C;
- Age over 40 years.

Women with close relatives who have had cervical cancer are at increased risk. Underlying immune disorders are an additional predisposing factor.

Anatomy and Epithelial Structure of the Cervix

The upper part of the cervix opens into the uterine cavity (internal os), while the lower part opens into the vagina (external os). The cervical canal connects the uterine cavity with the vaginal lumen. The shape of the cervix and the cervical canal differs in nulliparous, parous and postmenopausal women.

The cervix consists of a vaginal portion and a supravaginal portion. The inner surface of the vaginal portion is lined by stratified squamous epithelium (exocervix), which terminates at the external os. The inner portion of the cervical canal is lined by a single layer of glandular epithelium (endocervix). Cells of the cervical canal produce mucus that protects against infection and, at certain times in the menstrual cycle, limits the passage of sperm. Normally the cervical canal is closed; it opens slightly during menstruation to allow discharge. The condition of the cervical epithelium is an important parameter in the diagnosis of precancerous states and malignant disease.

Cervical cancer (CC) is a malignant tumor of the mucous membrane of the vaginal portion of the cervix and/or the cervical canal.

Epidemiology

Annually in the Russian Federation approximately 16,500 new cases of cervical cancer are diagnosed. Among female malignancies it ranks fifth. Over the past 15 years the incidence per 100,000 population has increased by nearly 25%.

Early-stage disease is identified in approximately 65% of patients. Cervical cancer more commonly affects females of middle age; the highest incidence is observed in the 30–34 year age group (24%). The average age of patients with cervical cancer is 54 years, with a trend toward a younger age at diagnosis.

Cervical cancer is one of the leading causes of cancer-related death among women. One-year mortality after diagnosis is approximately 15%. The highest mortality rate is observed in the 30–39 year age group (25%). With early detection, prognosis is favorable in approximately 92% of cases.

Background Cervical Diseases and Precancerous Conditions

Prior to the detection of malignant neoplasia, females often have background cervical diseases and/or precancerous conditions. Background diseases are characterized by normoplasia of epithelial cells — normal cell division, maturation, differentiation and desquamation without pathological changes. Three groups of benign background conditions are distinguished:

- Dys-hormonal: endometriosis, polyps, ectopia;
- Inflammatory: pseudo- and true cervical erosion, cervicitis;
- Post-traumatic: tears, scars of the cervix, eversion (ectropion).

Precancerous conditions are characterized by epithelial dysplasia — hyperplastic transformation, proliferation and impaired differentiation, maturation and exfoliation. These changes are confined within the basal membrane, which distinguishes them from invasive malignancies. Precancerous conditions with differing morphological patterns include:

- Dysplasia, classified into three grades depending on the depth of epithelial involvement: mild (CIN I), moderate (CIN II) and severe (CIN III);
- Leukoplakia with atypia;
- Erythroplakia;
- Adenomatosis.

Causes and Risk Factors of Cervical Cancer

Human papillomavirus (HPV) is one of the principal etiologic factors in the development of cervical cancer. Among all HPV-associated malignancies, cervical cancer accounts for approximately 69.1%.

More than 200 HPV genotypes have been identified; of these, over 120 infect humans. HPV types that infect the oral and anogenital mucosa mostly belong to the genus Alpha (α) and include types associated with high oncogenic risk.

HPV genotypes are stratified by oncogenic potential into high-risk and low-risk groups (some classifications include an intermediate group). HPV types 16 and 18 — responsible for approximately 71% of invasive cervical cancers — belong to the high-risk group. High-risk HPV types (including 16 and 18) are detected in a large proportion of patients with cervical carcinoma.

Because HPV infection is one of the most common sexually transmitted infections, it plays a central role in cervical carcinogenesis. Most sexually active individuals are exposed to HPV; adolescents and young females constitute a major risk group. Among females aged 15–30 years, approximately 18–20% are HPV carriers. After age 30, HPV prevalence decreases to approximately 8.6–9.9%, while detection of dysplasia and cervical cancer tends to increase and is often associated with HPV. Not all HPV-induced dysplasias progress to cancer; the risk is greater with moderate to severe dysplasia. The latent interval between infection with oncogenic HPV and development of cervical cancer may range from 5 to 30 years.

Additional risk factors include:

- Changing sexual partners more than 2–3 times per year;
- Initiation of sexual activity before age 16;
- Tobacco smoking;
- Impaired immunity (due to immunosuppressive therapy or HIV infection);
- Sexually transmitted infections (STIs);
- Excess body weight;
- Parity of three or more full-term pregnancies;
- First full-term pregnancy at age 17 or younger;
- Use of oral contraceptives for more than 5 years;
- Hereditary predisposition.

WHO data indicate that females who have had more than 10 sexual partners in their lifetime have a threefold increased risk of cervical cancer.

Clinical Symptoms of Cervical Cancer

In the initial stages the oncologic process is often asymptomatic and may be detected only during an extended gynecological examination. Signs that the tumor has penetrated beyond the epithelial layer into underlying tissues include:

- Bloody vaginal discharge or bleeding — contact (after intercourse) or spontaneous;
- Vaginal discharge that is clear or yellowish (leukorrhea);
- Prolonged, heavy and painful menstruation;
- Vaginal bleeding during menopause;
- Pain during sexual intercourse (dyspareunia);
- Painful urination;
- Pain in the vagina and the pelvis.

General systemic symptoms may include rapid weight loss, fatigue, frequent urination, low-grade fever (37–37.5 °C), and unilateral or bilateral leg edema. If you notice any of the signs above, consult a gynecologist.

Histological Types

Two principal histological groups of cervical cancer are distinguished: squamous cell carcinoma and adenocarcinoma. Each group includes several tumor types.

Squamous cell carcinoma, arising from the squamous epithelium of the ectocervix, accounts for approximately 8 out of 10 cases of cervical cancer. The common subtypes are:

- Well-differentiated (keratinizing) — generally associated with a favorable prognosis if detected early;
- Differentiated (non-keratinizing) — one of the most common and potentially dangerous types; symptoms are often pronounced;
- Poorly differentiated — the most aggressive variant;
- Basaloid type — occurs in around 15% of patients and is difficult to treat when advanced;
- Warty (condylomatous) — typically responds well to early treatment;
- Papillary — characterized by increased cellular atypia.

Adenocarcinoma affects the glandular epithelium of the endocervix and tends to infiltrate deeply into mucosal tissues. It is often asymptomatic in early stages and therefore can be difficult to diagnose.

Types of cervical adenocarcinoma include:

- Endophytic — the tumor grows within the cervical stroma, producing an inward appearance of the external os; difficult to detect and treat;
- Exophytic — exophytic lesions tend to arise from the vaginal portion and often have a lower degree of malignancy. They are more easily identified on clinical examination and often have a favorable outcome when detected early;
- Mixed — tumors showing features of both patterns; these are less common.

Rarely, sarcomas of the cervix (a third group) are diagnosed. Sarcomas are highly malignant, often asymptomatic in stages I–II, diagnosed late and are difficult to treat.

Staging of Cervical Cancer

Accurate staging of cervical cancer is essential for selecting the appropriate treatment strategy. Staging is based on the clinical extent of disease and commonly uses the FIGO and TNM (2009) classification systems.

- Stage 0: carcinoma in situ or localized precancerous epithelial abnormalities on the surface of the cervix;
- Stage I: the tumor is confined to the cervix and may extend to the uterus and regional lymph nodes. Approximately 47% of cervical cancers are detected at Stage I;
- Stage II: the tumor extends beyond the uterus to the upper part of the vagina but does not involve the pelvic wall or the lower third of the vagina. About 28% of cases are diagnosed at Stage II;
- Stage III: the tumor involves the lower third of the vagina and/or pelvic wall and may obstruct the ureters. Stage III accounts for approximately 21% of cases;
- Stage IV: the tumor invades the urinary bladder or rectum and/or has spread to distant organs. Stage IV comprises approximately 4% of diagnoses.

Each stage can be subdivided into sub-stages (e.g. IA1, IA2, IB1, etc.) which clinicians use to establish a precise diagnosis and treatment plan.

Main Stages of Diagnosis

The diagnostic workup for suspected cervical cancer includes collection of medical history, patient interview, gynecological examination and identification of clinical signs.

Laboratory methods used in the evaluation of cervical cancer include:

- Cytological examination (Pap smear) — a sample is taken from the cervix and examined cytologically;
- Testing for human papillomavirus (HPV) — a primary test for cervical cancer etiology, performed using various methods including PCR;
- Simple colposcopy — performed when suspicious changes are detected on examination or cytology; a microscope increases visualization (6–16×) to reveal subtle lesions;
- Extended colposcopy — the mucosa is stained with Lugol's iodine solution to highlight abnormal areas; sensitivity is approximately 80%;
- Targeted biopsy — performed when indicated; tissue samples from suspicious foci are taken for histological study and remain the main diagnostic method for confirming cancer type and stage;
- Measurement of the tumor marker SCC antigen — a specific protein produced by tumor cells that often increases in malignant disease.

Instrumental (imaging and endoscopic) methods used in screening and staging include:

- Ultrasound — a simple, minimally invasive and safe adjunctive method for determining the extent of disease;
- Cervicohysteroscopy — used for early detection of cervical cancer and a range of other conditions; diagnostic curettage may be performed during the procedure when indicated;
- Cystoscopy — endoscopic evaluation of the bladder, indicated when the tumor measures more than 4 cm, involves part of the vagina or when urinary symptoms suggest bladder involvement;

- Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) — employed to evaluate the degree of local invasion into adjacent tissues and organs and to assess regional lymph nodes;
- Rectosigmoidoscopy (rectoromanoscopy) — examination of the rectum, indicated with large tumors or suspected rectal invasion;
- Positron Emission Tomography (PET) — used to detect distant metastases;
- Bone scintigraphy — used when bone metastases are suspected.

Additional investigations may include intravenous urography, chest radiography and other studies as indicated. Routine blood tests are also performed.

Photodynamic Therapy

Photodynamic therapy (PDT) for cervical cancer is a form of photochemical treatment. Photosensitizing agents (photosensitizers) are administered to the patient, and the affected region is subsequently exposed to a specific wavelength of laser light.

The cytotoxic effect of PDT on tumor cells is based on the generation of reactive oxygen species within the cells, which damage cellular membranes and molecular structures leading to cell death. In addition, PDT damages the tumor's feeding blood vessels, resulting in ischemia and necrosis of the tumor focus.

Photodynamic therapy is effective for precancerous conditions, early-stage cervical cancer and non-invasive lesions. In most cases PDT is used as an alternative treatment method.

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