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Cervical Cancer Treatments: Current Obstacles and Future Prospects

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Abstract

Cervical cancer is the fourth most frequent malignancy in women worldwide, accounting for over 300,000 fatalities. Cervical cancer is caused by persistent infection with high-risk subtypes of the human papillomavirus. The viral oncoproteins E5, E6, and E7 work along with host factors to produce and maintain the malignant phenotype. Cervical cancer is mostly avoidable, and early detection leads to much higher survival rates. In high-income countries with robust vaccination and screening programs, the disease is infrequent. Women in low- and middle-income countries with inadequate resources commonly have advanced and untreatable disease, making it a fatal disease. Treatment options include surgery, chemotherapy, and radiotherapy, either individually or in combination.

Keywords: Cervical cancer; E6/ E7 oncoproteins

Introduction

Cervical cancer is the fourth most common cancer in women worldwide, and it has the fourth highest mortality rate among cancers in women. Most cases of cervical cancer are preventable with routine screening and treatment of precancerous lesions. As a result, most cervical cancer cases are diagnosed in women who live in regions with inadequate screening protocols.

Incidence and Mortality

Estimated new cases and deaths from cervical (uterine cervix) cancer in the United States in 2024:

New cases: 13,820.

Deaths: 4,360.

Initiation and progression of cervical cancer

Cervical cancer originates in the cervix which is the narrow opening into the uterus and is connected to the vagina through the endocervical canal. The cervix is divided into the ectocervix and endocervix and while the ectocervix is covered with stratified squamous epithelial cells, the endocervix consists of simple columnar epithelial cells. Stratified squamous and columnar epithelium form the squamocolumnar junction in the endocervical canal. The area where these regions meet is called the “transformation zone”, which consists of metaplastic epithelium that replaces the columnar lined epithelium of the endocervix. This zone is the most likely site for the development of cervical cancer because it is a major site of premalignant transformation via persistent HPV infection. There are two major histological sub-types of cervical cancer, squamous cell carcinoma (SCC) and adenocarcinoma. Whereas SCC develops from squamous cells in the ectocervix and accounts for approximately 75% of cervical carcinoma cases, adenocarcinoma originates from glandular cells that produce mucus in the endocervix. As SCC is the major subtype, this review will focus on describing its progression (Figure 1) [1].

Cervical cancer is a growth of cells that starts in the cervix. The cervix is the lower part of the uterus that connects to the vagina. Various strains of the human papillomavirus, also called HPV, play a role in causing most cervical cancers. HPV is a common infection that's passed through sexual contact. When exposed to HPV, the body's immune system typically prevents the virus from doing harm. In a small percentage of people, however, the virus survives for years. This contributes to the process that causes some cervical cells to become cancer cells (Figure 2).

You can reduce your risk of developing cervical cancer by having screening tests and receiving a vaccine that protects against HPV infection. When cervical cancer happens, it's often first treated with surgery to remove the cancer. Other treatments may include medicines to kill the cancer cells. Options might include chemotherapy and targeted therapy medicines. Radiation therapy with powerful energy beams also may be used. Sometimes treatment combines radiation with low-dose chemotherapy.

Symptoms

When it starts, cervical cancer might not cause symptoms. As it grows, cervical cancer might cause signs and symptoms, such as:

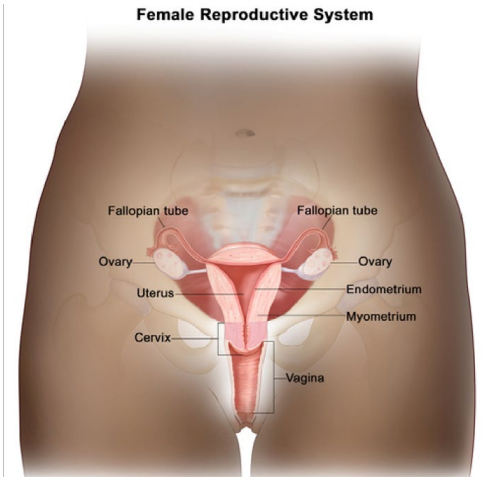

Figure 1: Anatomical diagram representing the female reproductive organs.

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- Vaginal bleeding after intercourse, between periods or after menopause.
- Menstrual bleeding that is heavier and lasts longer than usual.
- Watery, bloody vaginal discharge that may be heavy and have a foul odor.
- Pelvic pain or pain during intercourse [2].

Causes

Cervical cancer begins when healthy cells in the cervix develop changes in their DNA. A cell's DNA contains the instructions that tell a cell what to do. The changes tell the cells to multiply quickly. The cells continue living when healthy cells would die as part of their natural life cycle. This causes too many cells. The cells might form a mass called a tumor. The cells can invade and destroy healthy body tissue. In time, the cells can break away and spread to other parts of the body.

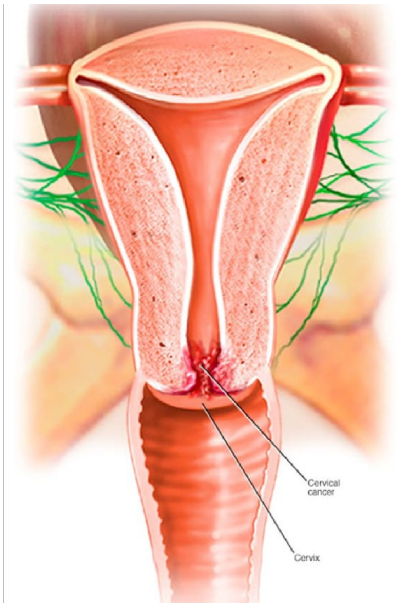

Figure 2: Anatomical diagram representing the female reproductive organs.

Most cervical cancers are caused by HPV. HPV is a common virus that's passed through sexual contact. For most people, the virus never causes problems. It usually goes away on its own. For some, though, the virus can cause changes in the cells that may lead to cancer (Figure 3).

Types of cervical cancer

Cervical cancer is divided into types based on the type of cell in which the cancer begins. The main types of cervical cancer are:

- **Squamous cell carcinoma:** This type of cervical cancer begins in thin, flatcells, called squamous cells. The squamous cells line the outer part of the cervix. Most cervical cancers are squamous cell carcinomas.
- **Adenocarcinoma:** This type of cervical cancer begins in the column-shapedgland cells that line the cervical canal.

Diagnosis and treatment

Diagnosis

Screening tests can help detect cervical cancer and precancerous cells that may one day develop into cervical cancer. Most medical organizations suggest beginning screening for cervical cancer and precancerous changes at age 21. The tests are usually repeated every few years [3].

Screening tests include

1) Pap test: During a Pap test, a member of your health care team scrapes and brushes cells from your cervix. The cells are then examined in a lab to check for cells that look different.

A Pap test can detect cancer cells in the cervix. It also can detect cells that have changes that increase the risk of cervical cancer. These are sometimes called precancerous cells [4].

2) HPV DNA test: The HPV DNA test involves testing cells from the cervix for infection with any of the types of HPV that are most likely to lead to cervical cancer [5].

Treatment

The type of treatment used for cervical cancer depends on the stage at diagnosis. More advanced cancers usually require a combination of

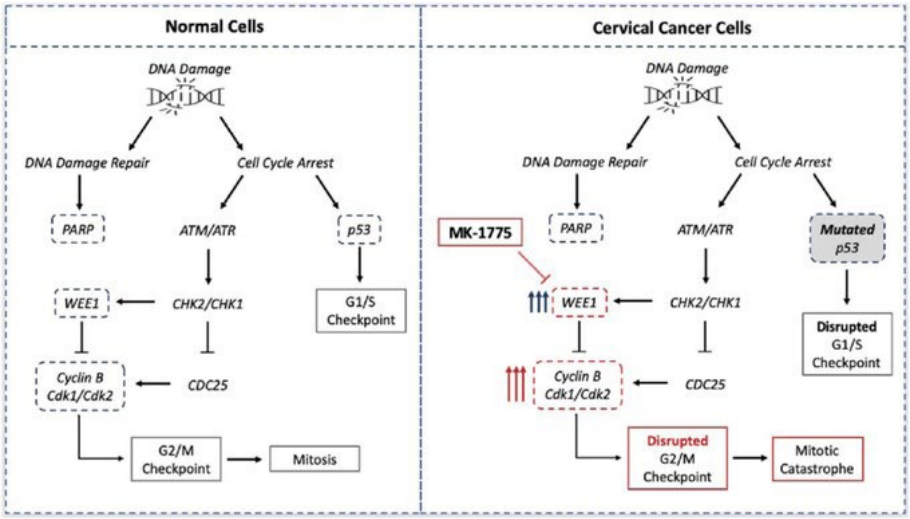

Figure 3: Flow chart of normal cells and cervical cancer cells.

treatments. Standard treatment options include:

Surgery, Radiation therapy, Chemotherapy and other medications [6].

Surgery

- Small cervical cancers that haven't grown beyond the cervix are typically treated with surgery. The size of your cancer, its stage and whether you would like to consider becoming pregnant in the future will determine which operation is best for you.
- Options might include:
- Surgery to cut away the cancer Only
- Surgery to remove the cervix, called a trachelectomy
- Surgery to remove the cervix and uterus, called a hysterectomy [7].

Radiation therapy

Radiation therapy uses powerful energy beams to kill cancer cells. The energy can come from X-rays, protons or other sources. Radiation therapy is often combined with chemotherapy as the primary treatment for cervical cancers that have grown beyond the cervix. It also can be used after surgery if there's an increased risk that the cancer will come back.

Radiation therapy can be given:

- Externally, called external beam radiation therapy. A radiation beam is directed at the affected area of the body.
- Internally, called brachytherapy. A device filled with radioactive material is placed inside your vagina, usually for only a few minutes.
- Both externally and internally [8].

Chemotherapy

Chemotherapy uses strong medicines to kill cancer cells. For cervical cancer that has spread beyond the cervix, low doses of chemotherapy are often combined with radiation therapy. This is because chemotherapy may enhance the effects of the radiation. Higher doses of chemotherapy might be recommended to help control symptoms of very advanced cancer [9].

Chemotherapy may be used before surgery to reduce the size of the cancer [10].

Targeted therapy

Targeted therapy uses medicines that attack specific chemicals in the cancer cells. By blocking these chemicals, targeted treatments can cause cancer cells to die. Targeted therapy is usually combined with chemotherapy. It might be an option for advanced cervical cancer [11].

Immunotherapy

Immunotherapy is a treatment with medicine that helps your immune system kill cancer cells. Your immune system fights off diseases by attacking germs and other cells that shouldn't be in your body. Cancer cells survive by hiding from the immune system. Immunotherapy helps the immune system cells find and kill the cancer cells. For cervical cancer, immunotherapy might be considered when the cancer is advanced and other treatments aren't working [12].

Prevention

Primary prevention

Primary prevention essentially includes healthy lifestyles, such as abstinence and safe sex, cessation of smoking, and HPV vaccination. Changing sex practices e.g. condom use would reduce the spread of both HIV and HPV but this is challenging to implement.

Secondary prevention

Secondary prevention aims to detect and treat preinvasive cervical lesions, before they become invasive. There are several secondary prevention modalities.

Future prospects

Though cervical carcinoma is a largely preventable disease, an average of 4 248 women in South Africa die annually from this disease. Research shows that well- implemented, non-opportunistic national cervical screening programs can significantly reduce the morbidity and mortality rates attributed to cervical cancer. According to the WHO, successful screening programs require >80% coverage, appropriate followup and management of patients with positive tests, effective links between screening diagnosis and treatment services, high quality care and adequate resources. This applies to all screening strategies viz. cytology, HPV and VIA/VILI. Currently, there is still no effective population-wide screening programme in South Africa. In several regions partial screening takes place and in the private sector opportunistic screening is commonly practised. A new cervical cancer control policy is due to be released soon, combining new technologies with current screening strategies. Several cytologic modalities are available, as an alternative to conventional cervical smears being viewed by technologists under the microscope. Liquid based cytology (LBC) is a different method of preparing cytologic specimens for evaluation under the microscope. Although this technology has been available for the past 15-20 years, it has not been adopted by the public sector laboratory as it is costly. Some, but not all studies, have shown improved specimen adequacy and detection of abnormalities with LBC that may offset the cost. The public sector laboratory is planning to introduce LBC. Computer assisted screening of LBC smears should assist cytotechnologists with their worked [13].

Conclusion

Cervical cancer prevention services should be linked with cervical cancer treatment and palliative care services. From the experience of the ACCP, collaborators, and in-country partners, two overall strategies can be described to reduce the burden of disease from cervical cancer.

For countries with no radiotherapy, radical surgery, or chemotherapy, the focus should be to:

- Establish and strengthen cervical cancer prevention services to reduce the future need for resource-intensive treatment services.
- Establish and strengthen palliative care services at all levels of health facilities, including community care.
- Plan and start investing in centralized basic treatment services for cervical cancer.
- For countries with limited cervical cancer treatment services, the focus should be to:
- Establish and strengthen cervical cancer prevention services to reduce the future need for resource-intensive treatment services.
- Establish and strengthen palliative care services at all levels of health facilities, including community care.

- Strengthen and increase the availability of radical surgery, if such potential exists.

- Strengthen and increase access to available radiotherapy services.

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