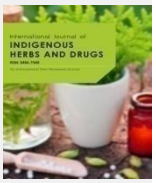
Review Article

International Journal of Indigenous Herbs and Drugs
Content Available at www.saap.org.in ISSN: 2456-7345



# CONTEMPORARY APPROACHES TO CERVICAL CANCER MANAGEMENT

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***Article Info***
*Article History*
Received on: 04-06-2025
Revised on: 17-06-2025
Accepted on: 24-07-2025

**Abstract**

Cervical cancer represents a widespread global health concern, responsible for considerable morbidity and mortality among women around the world. The illness is mainly triggered by long-lasting infection with high-risk human papillomavirus (HPV) types. Although effective preventive measures such as HPV vaccination and screening are available, cervical cancer persists as a primary cause of cancer-related fatalities among women in low- and middleincome nations. Recent progress in understanding the biology of cervical cancer has prompted the creation of new therapeutic methods, encompassing targeted therapies and immunotherapies. These cutting-edge treatments have displayed encouraging outcomes in enhancing patient results, especially in advanced-stage and recurrent cases. This review intends to deliver a thorough summary of the existing knowledge regarding cervical cancer, encompassing its epidemiology, prevention methods, diagnostic techniques, and treatment possibilities. We also examine recent advancements in cervical cancer research and their potential effects on patient care.

***Keywords:*** cervical cancer, HPV, immuno therapy, screening, chemotherapy.



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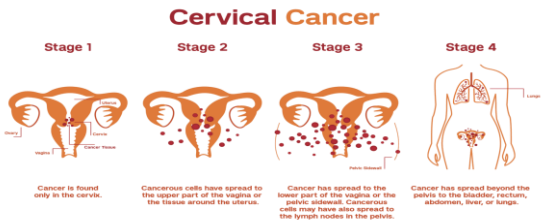
## Introduction

Cancer is the fourth most frequently diagnosed cancer in women globally. Worldwide, cervical cancer ranks as the second leading cause of cancer deaths among women aged 20–39 and continues to account for more. Human papillomavirus (HPV) infection leads to substantial disability-adjusted life years lost annually [1]. More than 85% of cervical cancer deaths occur in 43 developing countries. Major risk factors include a history of human papillomavirus (HPV), early sexual initiation, multiple sexual partners, high-risk sexual conduct, immunosuppression, history of sexually transmitted infections (STIs), vulvar or vaginal dysplasia, and a history of tobacco use. Smoking status, duration, and quantity smoked correlate with double the risk of high-grade lower genital tract dysplasia after accounting for HPV status, while quitting smoking has been shown to lead to a two-fold reduction in risk. Moreover, the absence of screening represents a significant risk factor. Ninety percent of cervical cancer cases arise in low- and middle-income nations (LMIC). It is the fourth most prevalent cancer among women globally [2], following breast, colorectal, and lung cancer. The implementation of screening tests using the Papanicolaou smear (Pap smear) since 1971 and the human papillomavirus (HPV) vaccination since 2006 has resulted in a marked decline in the incidence of cervical intraepithelial neoplasms (CIN) and cervical cancer in developed nations. Cervical cancer is now the thirteenth most frequent cancer in women in developed countries like Germany However, there has been no noteworthy decline in mortality or morbidity over the past decade; treatment strategies remain quite varied.




## Stages of cervical cancer

Screening for women over age 65 is not recommended for those who tested negative through cytology three times or had negative hrHPV/co tests twice [3]. Women who have undergone hysterectomy or trachelectomy do not require screening unless they have a history of highgrade cervical lesions or cancer . Socioeconomic status significantly

influences screening success, as many women who are uninsured, belong to minority groups, are immigrants, have limited education, or do not receive routine primary care are less likely to be screened [4]. Screening is essential in preventing cervical cancer, as surgical intervention is the only effective treatment for early-stage disease. Surgical options for cervical cancer depend on the stage and include conization, simple hysterectomy, radical hysterectomy, or radical trachelectomy with pelvic lymphadenectomy [5].

## Pathogenesis and risk factors

Cervical cancer arises when the cells lining the cervix undergo abnormal changes and begin to multiply uncontrollably [6]. The primary cause of these cellular changes is a persistent infection with high-risk strains of the human papillomavirus (HPV), particularly types 16 and 18. While HPV infection is common and often cleared by the immune system, in some cases, it can persist and lead to the development of precancerous lesions.[7] Over time, if these lesions are not detected and treated, they can progress to invasive cervical cancer. The transformation from normal cervical epithelium to cancer involves multiple genetic and epigenetic changes, including alterations in tumor suppressor genes and cell cycle regulation.

Several risk factors can increase the likelihood of developing cervical cancer. These include early onset of sexual activity, having multiple sexual partners, and a partner with a history of multiple sexual partners, all of which increase exposure to HPV. [8]Smoking is another significant risk factor, as tobacco byproducts can damage the DNA of cervical cells and impair immune response. Long-term use of oral contraceptives has also been associated with a slightly increased risk.[9] Additionally, women with weakened immune systems, such as those with HIV/AIDS, are more susceptible to persistent HPV infections. Poor hygiene, low socioeconomic status, and limited access to regular Pap smear screening also contribute to delayed diagnosis and treatment, raising the risk of developing cervical cancer[10].

## Diagnosis investigation and preventions

### Micro invasive disease

Diagnosis of Stages IA1 and IA2 is determined through the microscopic evaluation of a cone biopsy sample, collected via LEEP or cold knife conization, which encompasses the entire lesion. It may also be established based on a specimen from a trachelectomy or hysterectomy. The depth of invasion must not exceed 3 or 5 mm, respectively, from the epithelial base. The horizontal dimension is no longer a factor in the 2018 revision because it has not been demonstrated to influence survival. Attention should be given to lymphovascular space involvement, which does not change the stage but may influence the treatment strategy. The margins must be reported as negative for disease. If the cone biopsy margins are positive for invasive cancer, the patient is categorized under Stage IB1.

### Invasive disease

In cases where visible lesions are present, a punch biopsy typically suffices for diagnosis, but if it is inadequate, a small loop biopsy or cone may be necessary. Clinical evaluation is the initial step in the process of staging allocation. FIGO 2018 staging allows for the utilization of any imaging techniques based on available resources, such as ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET), to offer further insights into tumor size, nodal involvement, and local or systemic dissemination. MRI is the most effective approach for radiologic evaluation of primary tumors exceeding 10 mm. Nevertheless, ultrasound has also demonstrated commendable diagnostic accuracy when performed by experts. The imaging method utilized for staging should be documented for future assessments. Imaging can reveal additional prognostic elements that may influence the selection of the most suitable treatment option. [11.] test in comparison to traditional cytology or colposcopy .The research has indicated the safe and sensitive effectiveness of self-sampling for the HPV test, alongside its advantages in LMIC due to its simplistic and user-friendly nature and its physical and emotional comfort [12]. Consequently, Detection of cervical cancer [13]. HPV vaccination serves as an effective primary prevention measure against cervical cancer.

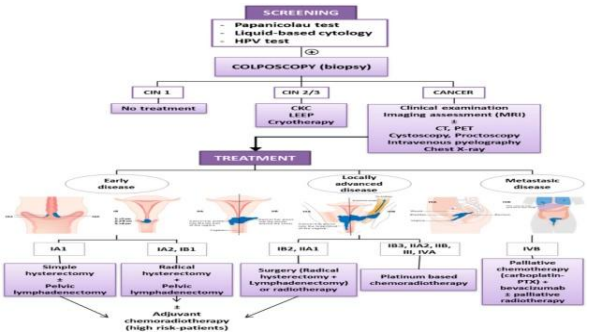
In 2007,the recommendations of the Standing Commission on Vaccination (STIKO) [14]introduced the precautionary HPV

vaccination, which currently promotes vaccination for girls aged 9 to 14 years; since 2018, it has also been endorsed for boys within this age range .The prophylactic benefits of the HPV vaccination concerning vaccine-type-specific anogenital diseases have also been demonstrated in women and men aged 14–45 years [15] The Centers for Disease Control and Prevention (CDC) in the United States advises routine HPV vaccination at ages 11 or 12, with the possibility of starting vaccination at age 9, a catch-up vaccination up to age 26, and possible vaccination for adults ages 27 to 45 [16,17].

## Current techniques for cervical cancer screening

The reliability of Pap tests in identifying intraepithelial neoplasia and early-stage cervical cancer ranges from 50% to 87%, with around 24–32% of women receiving negative results for invasive cervical cancer [18]. These results highlight the necessity for alternative screening methods. Studies have established a connection between cervical cancer and human papillomavirus (HPV), which is more commonly found in women over 50 years old, decreasing from 11. 1% to 2. 9%.

The occurrence of HPV shows considerable variation, with rates from 10% in China to 46% in Italy. Chronic HPV infection elevates the likelihood of cervical cancer by ten times, making it essential to pinpoint high-risk HPV strains and create new screening approaches. HPV screening




serves as a dependable technique for identifying cervical cancer in women at its early stages and provides superior outcomes compared to cytological testing [19]. The diagnostic efficacy of this test may be enhanced by triaging women who are positive for HPV.

## Cervical cancer disease management

Primary and secondary methods to avert cervical cancer continue to be crucial in alleviating the burden of the disease, and a considerable amount has been documented regarding this. Thus, this review concentrates on the treatment alternatives for cervical cancer. Cervical cancer in its early stages is frequently asymptomatic and can be identified during a routine screening or pelvic examination. The most prevalent symptoms consist of heavy or irregular vaginal bleeding, particularly following sexual intercourse Some women might show a vaginal discharge that can be watery, mucoid, or purulent and foul-smelling; however, this is seldom observed without other accompanying symptoms. In more advanced cases, patients may suffer from swelling of the lower limbs, flank pain, as well as discomfort in the pelvic area or lower back. Furthermore, bowel and/or bladder related issues such as changes in urine pressure or the expulsion of urine and/or feces via the vagina suggest invasion of the bladder and rectum respectively. [20]

### Treatment of cervical cancer

### Treatment of cervical cancer

As indicated above, the stage and extent of cervical cancer progression determines the treatment strategy needed and may include one or a combination of surgery, radiation and chemotherapy.

### Surgical treatment

Surgery usually involves physical removal of cancer, and is used in the early stages to fight various crayfish and is successful. However, it can also be used to remove metastatic tissue. Currently, types of surgical procedures performed to treat cervical cancer include complete hysterectomy, radical hysterectomy, electrosurgical impact procedures (LEEP), degradation, shitting, cryosurgical surgery. The choice of surgical procedures depends largely on the stage and extent of distribution of the disease. otal hysterectomy with or without salpingo-oophorectomy (the removal of one or both ovaries), remains the treatment of choice for women who have completed childbearing. Radical hysterectomy is most commonly used for larger cervical cancer lesions (up to 4 cm in size) and involves complete resection of the uterus, cervix, parametria, and cuff of the upper vagina. The findings of the Laparoscopic Approach to Cervical Cancer (LACC) trial revealed that radical hysterectomy performed using laparoscopy was associated with an increased rate of recurrence, loss of fertility and potential urinary dysfunction in the long-term.

### Radiotherapy

A key treatment for cervical cancer is radiotherapy, which targets and shrinks tumours using high-energy x-rays Three primary forms of radiation therapy are employed: The most popular type of radiotherapy is called External Beam Radiation Therapy (EBRT), which also includes Intensity Modulated Radiotherapy (IMRT) and Brachytherapy (internal RT). EBRT targets the tumor with radiation beams that are directed from outside the body. IMRT is a more sophisticated method that can be used on both cancerous and noncancerous tumors since it can customize radiation beams to fit the contour of the tumor. Brachytherapy is either inserting a radioactive implant at the tumor site while preserving surrounding tissues, or administering a high dosage of radiation directly to the tumor. Better diagnostic techniques, including as CT and MRI scans, help assess the tumor, the extent of invasion, and metastases, which helps to improve radiotherapy planning.

- **Immuno therapy**
  Beyond ICI, multiple immunotherapy strategies are being assessed in metastatic cervical cancer. Cancer vaccines and cell-based therapies are some of the most promising options. The well-established role of HPV in cervical cancer makes HPV-associated oncoproteins an appealing target for vaccine-based treatments. ADXS11-001 is a live attenuated Listeria monocytogenes vector vaccine aimed at delivering an HPV 16 E7 fusion protein that targets HPV-transformed cells. This would elicit an antitumoral T cell response and may overcome immune tolerance.

## Choice of treatment

- Surgery is beneficial for the treatment of most cervical cancer. If the cancer has invaded nearby tissue, one of two types of hysterectomy may be necessary
- In some cases, a straightforward hysterectomy that removes the uterus and cervix will suffice.

### Radical Hysterectomy

It is essential to excise the primary connective tissue (parametrium) and ligaments along with the upper portion of the vagina. If needed, either of these procedures may be performed alongside the removal of the fallopian tubes and ovaries, resulting in infertility, and the removal of the ovaries induces menopause in females. Lymph nodes may also be removed during the procedure.

### Radiation Therapy

It may also be utilized in treating cervical cancer, often incombination with surgery. This is applicable if the cancer is encroaching and spreading from the surface of the

cervix.

**Brachytherapy**

Employs implanted radioactive rods or pellets to concentrate the radiation on the cancer and significantly minimize side effects. Pelvic radiation therapy may also induce premature menopause, bladder irritation, or a narrowing of the vagina due to scar tissue accumulation.

## New therapies in cervical cancer

**Immunotherapy**

Immunotherapy has emerged as a promising approach in treating cervical cancer. Checkpoint inhibitors, such as pembrolizumab and nivolumab, have shown significant activity in advanced cervical cancer. These agents work by releasing the brakes on the immune system, allowing it to attack cancer cells more effectively

**Pembrolizumab:** An anti-PD-1 antibody that has shown Significant activity in advanced cervical cancer.

## Targeted Therapy

Targeted therapies, such as bevacizumab, have been shown to improve outcomes in cervical cancer. Bevacizumab targets the vascular endothelial growth factor (VEGF) pathway, which plays a critical role in tumor angiogenesis. Other targeted agents, such as tyrosine kinase inhibitors, are also being investigated.

**Antibody-Drug Conjugates (ADCs)**

ADCs, such as tisotumab vedotin, have demonstrated encouraging activity in cervical cancer. ADCs work by delivering a cytotoxic payload directly to cancer cells, minimizing harm to healthy tissues.

**Combination Therapies**

Combination regimens, such as chemotherapy plus immunotherapy or targeted therapy, are being explored to improve outcomes in cervical cancer. These combinations aim to enhance anti-tumor activity while minimizing toxicity.

**Adoptive Cell Therapy**

Adoptive cell therapy, which involves transferring autologous T cells into patients, has shown promise in treating cervical cancer. This approach enables the immune system to recognize and attack cancer cells more effectively.

**Gene Therapy**

Gene therapy, which involves introducing genes into cells to fight cancer, is being investigated in cervical cancer. This approach aims to enhance anti-tumor immunity and improve treatment outcomes.

**HPV-targeted gene therapy**: Gene therapy approaches targeting HPV are being explored as a potential treatment for cervical cancer.

**Nanoparticle-Based Therapies**

1. **Nanoparticle-based delivery of anti-cancer agents:** Nanoparticles can be used to deliver anti-cancer agents directly to cancer cells, minimizing harm to healthy tissues.
2. **Nanoparticle-based immunotherapy:** Nanoparticles can be used to deliver immunotherapeutic agents directly to cancer cells, enhancing anti-tumor immune

- **Other Advanced Therapies**
  1. **Photodynamic therapy:** A therapy that uses light to activate anti-cancer agents.
  2. **High-intensity focused ultrasound (HIFU):** A therapy that uses sound waves to heat and destroy cancer cells.
  3. **Cryotherapy:** A therapy that uses freezing temperatures to destroy cancer cells

**Targeted Therapies in Cervical Cancer**

Cervical cancer is a multifaceted and varied disease that necessitates tailored treatment strategies. Targeted therapies have emerged as an encouraging approach for managing cervical cancer, providing enhanced effectiveness and decreased toxicity compared to conventional chemotherapy.

## Conclusion

Cervical cancer is a complex and heterogeneous disease that requiresa multifaceted approach for prevention, diagnosis, and treatment. While significant progress has been made in understanding the biology of cervical cancer, there is still a need for improved prevention strategies, early detection methods, and effective treatments. The development of targeted therapies, immunotherapies, and combination regimens has shown promise in improving outcomes for patients with cervical cancer. However, further research is needed to fully explore the potential of these approaches and to identify the most effective treatment strategies for specific patient populations. In addition, there is a need for increased awareness and education about cervical cancer, particularly in low- and middle-income countries where access to screening and treatment is limited. Healthcare providers, policymakers, and patients must work together to address the disparities in cervical cancer outcomes and to ensure that all women have access to effective prevention and treatment strategies. Ultimately, the goal of cervical cancer research and treatment is to reduce the incidence and mortality of this disease, and to improve the quality of life for women affected by it. With continued advances in research, education, and healthcare delivery, we can work towards a future where cervical cancer is no longer a significant threat to women's health

## Author Contributions

All authors are contributed equally

## Financial Support

None

## Declaration of Competing Interest

The Authors have no Conflicts of Interest to Declare.

## Acknowledgements

None.

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