



A Broad Review Of Current Approaches And Future Advancements In Cervical Cancer Management

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Abstract:- Cervical cancer is a significant worldwide health concern. With the intention of advising medical professionals and researchers on current advancements and potential future paths in this area, this comprehensive analysis provides an overview of the available and developing cervical cancer therapy options. Surgical techniques, radiation therapy, and chemotherapy are the current treatment options for cervical cancer; they are often used in combination, depending on the disease's stage and severity. However, in situations that are advanced or recurrent, these traditional therapies may not be effective and are often associated with serious adverse effects. As a result, the need for creative treatment approaches is rising. Recent developments in cervical cancer treatment include a variety of cutting-edge strategies including gene-based therapy, immunotherapy, and targeted therapy. Clinical trials have shown promising outcomes for targeted medicines, such as those that inhibit Vascular Endothelial Growth Factor (VEGF) and Epidermal Growth Factor Receptor (EGFR), particularly when paired with conventional medications. Immunotherapy has revolutionized cancer treatment and has great potential for people with cervical cancer, especially when it comes to immune checkpoint inhibitors. Furthermore, gene therapy approaches that involve gene editing and oncolytic viruses provide novel ways to eradicate cancer cells while protecting healthy tissue. Patient outcomes for cervical cancer might be significantly improved in the next years by incorporating these novel medicines into routine medical care. To address medication resistance concerns, find predictive biomarkers for patient selection, and enhance treatment regimens, further study is required. In order to get these new treatments from lab research to clinical practice and eventually lessen the global effect of cervical cancer, partnerships between medical professionals, academics, and the pharmaceutical industry will be essential.

Keywords:- HPV, Chemotherapy, Immunotherapy, Targeted therapy.

1. INTRODUCTION

Cervical cancer is the fourth most common malignancy in women worldwide, accounting for over 340,000 deaths annually(1). Human papillomavirus (HPV) infection is the main cause of cervical cancer. According to studies, 99.7% of occurrences of cervical cancer are caused by a chronic HPV infection. Furthermore, there is strong evidence that women who are infected with the Human Immunodeficiency Virus (HIV) are more likely to get HPV, which raises their risk of cervical cancer(2). Cervical cancer is really about six times more common in women with HIV than in those without the virus. Staging of the illness is crucial before starting any therapy, and it is carried out in accordance with the International Federation of Gynecology and Obstetrics' (FIGO) criteria(3). Cervical cancer is categorized using this staging approach from stage I to stage IV based on the size of the tumor, the depth of tissue invasion, and the degree of the disease's body spread. Radiation therapy and surgery are the recommended treatment options for cervical cancer in its early stages. On the other hand, radiation therapy and cisplatin-based chemotherapy are often used in the treatment of advanced stages, and if the spread is kept to a minimum, this combination may be curative(4). The use of pharmaceuticals to treat cervical cancer has advanced significantly over time. These developments have enhanced the safety and efficacy of available treatments and raised patient survival rates. Presenting a thorough summary of the pharmacological drugs presently utilized to treat cervical cancer is the main goal of this study(5).

Survival rates

The chart shows the survival rate (%) for cervical cancer across the 11 Population Based Cancer Registries (PBCRs)

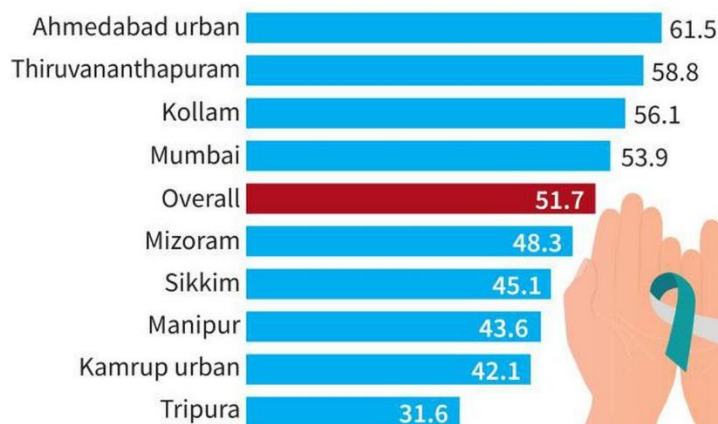


Figure 1 Survival rates of Cervical Cancer in India

2. CERVICAL CANCER DISEASE MANAGEMENT

A comprehensive strategy that is tailored to the patient's unique requirements and the disease's stage of advancement is often needed for the care of cervical cancer(6). The following are the main components of cervical cancer treatment:

2.1. Prevention

Targeting the high-risk strains of HPV, the HPV vaccine is a crucial preventative intervention that reduces the risk of getting cervical cancer(7). In order to detect precancerous changes early and provide timely and efficient treatment, routine cervical cancer screening techniques including Pap smear and HPV detection tests are essential(8).

2.2. Treatment

Cervical cancer treatment plans are determined by a number of variables, such as the disease's stage, its spread, the patient's overall health, and personal treatment preferences. Surgical intervention, radiation treatment,

chemotherapy, and the use of targeted therapeutic medicines are among the frequently used therapeutic techniques(9). Furthermore, immunotherapy specifically, the use of immune checkpoint inhibitors is becoming more widely acknowledged as a viable and successful therapeutic option for the management of cervical cancer(10).

2.3. Palliative Care

Palliative care is essential for controlling symptoms, improving the patient's quality of life, and providing emotional and psychological support to patients and their families in instances of advanced or recurring cervical cancer when there is little chance of a full recovery(11).

2.4. Surveillance

Patients are scheduled for regular follow-up appointments after treatment is finished to monitor for any indications that the cancer has returned or progressed(12). Physical exams, diagnostic imaging procedures like CT or MRI scans, and laboratory tests like tumor marker analyses may all be part of the monitoring during these visits(13).

2.5. Supportive Care

In order to address the physical, emotional, and social aspects of a patient's well-being, supportive care is essential throughout the whole illness treatment process. This might include offering access to a range of community support services, dietary advice, psychiatric counseling, and efficient pain management(14). Generally speaking, the goal of a well-coordinated, patient-centered approach to cervical cancer treatment is to maximize health results while minimizing side effects and preserving the patient's quality of life. To provide comprehensive and effective treatment for patients with cervical cancer, close collaboration between medical experts such as gynecologists, oncologists, radiation specialists, and supportive care teams is essential(15). For the majority of cervical malignancies, systemic platinum-based chemotherapy and radiation therapy are usually the main therapeutic modalities. When compared to radiation alone, this combination of treatments has shown better outcomes in terms of total patient survival rates and disease-free survival. Although they are often controllable, side effects are more likely to occur when chemotherapy is added to the treatment regimen(16). The patient's risk of illness recurrence determines whether further therapies are needed; patients at greater risk often need chemoradiotherapy. Platinum-based treatments have been shown in several trials to be successful when used in combination with chemotherapy and radiation therapy to increase the survival rate of patients with cervical cancer, highlighting its significance in treatment planning for all patients(17). Furthermore, studies have shown that in patients with recurrent cervical cancer after first-line platinum-based chemotherapy, cemiplimab significantly improves survival rates when compared to single-agent treatment. A major advancement in the treatment of this difficult disease was made when it was discovered that the cemiplimab group had a greater response rate than the chemotherapy group. There is no widely accepted standard therapy for people with stage IVB cervical cancer, in contrast to those with locally progressed illness(18). Chemotherapy may be helpful for patients with stage IVB or recurring cervical cancer who are not good candidates for radiation treatment or major surgery. However, it has been shown that traditional chemotherapy is only partially successful in eradicating the main cervical tumor and any metastases(19). For these advanced-stage patients, combining chemotherapy and radiation treatment has been shown to enhance survival rates.

3. CURRENT TREATMENT METHODS FOR CERVICAL CANCER

3.1. Surgery

In the treatment of cervical cancer, particularly in its early stages, surgical intervention is crucial. The uterus, cervix, and surrounding tissues are removed during a radical hysterectomy, the most frequent surgical procedure(20). To assess the degree of cancer spread, the pelvic lymph nodes may sometimes be removed as well. Depending on the size of the tumor and the stage of the cancer, less invasive procedures like cone biopsy or trachelectomy may be an option for women who want to preserve their fertility. Especially at more advanced phases, surgery is often used in conjunction with other therapeutic approaches like radiation or chemotherapy to

increase the efficacy of treatment. Surgery has the potential to cure early-stage cervical cancer, but it also carries risks and problems, such as bleeding, infection, and damage to nearby structures(21). Therefore, to guarantee the best results and lower the risk of problems, careful patient evaluation and pre-operative preparation are crucial. All things considered, surgical therapy is still an essential part of managing cervical cancer as it may help patients recover and live better lives. Because surgery may physically remove cancerous tissues, it is still a commonly used and successful treatment for a variety of early-stage malignancies(22). Additionally, it is used to eliminate illness metastatic locations. Despite its short- and long-term negative effects, radical surgery is still the standard of care for early cervical cancer. Typically, this involves an open radical hysterectomy with bilateral pelvic lymph node dissection. For women of reproductive age with early-stage cervical cancer, a more cautious surgical approach is advised. Trachelectomy, Loop Electrosurgical Excision Procedure (LEEP), and conization are available fertility-preserving procedures(23). Although it is currently being studied, the use of less invasive and fertility-sparing operations in patients with good prognostic characteristics and low-stage illness is not yet advised for normal clinical practice. Before, minimally invasive surgery (MIS) was thought to be the best option for cervical cancer procedures(24). However, new research has shown that MIS has lower survival rates than open surgery, which has led to a return to open abdominal surgery as the preferred treatment method. Patients with stage IVB cervical cancer have shown greater survival advantages when surgery and chemoradiotherapy are combined; the median survival length increased to about 32 months, compared to around 19 months for those who did not have surgery(25). By reducing symptoms like pain and bleeding, this integrated strategy not only improves local disease management but also improves the patient's quality of life and lengthens survival(26).

3.2. Radiotherapy

One important treatment option for cervical cancer is radiotherapy, which is often combined with other therapeutic modalities including chemotherapy or surgery. High-energy radiation beams are used to destroy cancer cells while attempting to cause the least amount of harm to surrounding healthy tissues(27). External Beam Radiation Therapy (EBRT) or brachytherapy are two methods of administering radiation, depending on the particular situation and patient characteristics. In addition to managing symptoms and improving the patient's quality of life in late stages, this therapy may be able to cure cervical cancer in its early stages. Treatments for cervical cancer have become more accurate and successful because to technological developments like Image-Guided Radiation Therapy (IGRT) and Intensity-Modulated Radiotherapy (IMRT). However, gastrointestinal issues, skin irritation, and exhaustion are typical side effects, therefore supportive care is essential for patient comfort throughout therapy(28). When it comes to treating cervical cancer, high-energy beam radiation is essential. Brachytherapy (internal radiation therapy), intensity-modulated radiation treatment (IMRT), and external beam radiation therapy (EBRT) are the three primary forms of radiotherapy that are used. Advanced imaging methods such as CT and MRI scans allow physicians to more accurately determine the tumor's size, spread, and metastatic extent. This facilitates efficient radiation planning(29). One of the most popular types of radiation for treating cancer is EBRT, which involves directing high-energy beams toward the tumor from outside the body(28). IMRT is a contemporary method that enhances accuracy and reduces harm to surrounding healthy tissues by modifying the intensity of photon or proton beams to fit the form of the tumor. In order to directly provide a high dosage of radiation while preserving nearby tissues, brachytherapy involves positioning a radioactive device within or close to the tumor(30). Despite these improvements, radiation may still have a number of adverse effects, including skin problems, lymphedema, pelvic discomfort, diarrhea, cramping in the abdomen, and sexual dysfunction. With failure rates between 20 and 50 percent, radiotherapy may not always be sufficient to manage the illness. It is often used in conjunction with chemotherapy to boost its efficacy, particularly in instances of advanced cervical cancer(31).

3.3. Chemotherapy

Chemotherapy is still a key component of cervical cancer treatment. It works by using certain medications to either kill cancer cells or stop them from proliferating and spreading. Depending on the disease's stage and severity, chemotherapy may be administered alone or in conjunction with other therapeutic modalities like surgery or radiation therapy(32). Chemotherapy is essential, particularly for treating advanced or recurring

cervical cancer, despite the possibility of adverse effects because of its impact on healthy cells. In order to enhance patient outcomes and reduce side effects, current research is focused on creating chemotherapy tactics that are more targeted and less dangerous(33). One important component of the therapeutic treatment of cervical cancer is chemotherapy. It is often given in conjunction with radiation or after surgery. Chemotherapy may be the main treatment for locally advanced cancer in some circumstances. Depending on the patient's condition, the treatment strategy may include single, dual, or triple medication regimens. Numerous chemotherapeutic medicines, including platinum-based medications like carboplatin and cisplatin, as well as other medications like gemcitabine, topotecan, paclitaxel, vinorelbine, ifosfamide, and more recent targeted medications like bevacizumab, have shown promise in treating cervical cancer(34). Cisplatin has become the most popular and successful medication for treating cervical cancer, despite the fact that these medications are also good at controlling the illness and its symptoms. Cisplatin is usually administered at a dosage of 50 mg/m² every three weeks, with a response rate of up to 38%(35). But even with a favorable initial reaction, many patients later become resistant to cisplatin. Because of this, cisplatin has shown greater therapeutic advantages when combined with other chemotherapeutic drugs than when used alone. For example, the response rate to cisplatin monotherapy was around 19%, but when combined with paclitaxel, it rose to about 36%. Similarly, topotecan and cisplatin together have shown comparable enhanced results. Chemotherapy is thus still a crucial component of the treatment of cervical cancer, often used in conjunction with surgery and radiation therapy(36). Although cisplatin is a very successful single-agent treatment, its ability to effectively manage the illness is greatly increased when combined with additional medications such as topotecan or paclitaxel(37).

3.4. Immunotherapy

Cervical cancer immunotherapy targets and destroys cancer cells by using the body's immune system. Immuno-checkpoint inhibitors are medications used in this approach that target certain proteins that hinder the immune system's ability to fight cancer(38). The management of cervical cancer has shown notable efficacy using inhibitors of programmed cell death protein 1 (PD-1) and programmed death ligand 1 (PD-L1). These drugs aid in immune cell activation, which improves their capacity to recognize and eliminate cancer cells(39). Immunotherapy has become a useful cervical cancer therapeutic option, particularly for individuals who have not responded to conventional treatments. Patients whose illness worsened after receiving platinum-based chemotherapy had few alternatives for treatment in the past. The treatment of cervical cancer has significantly improved with the advent of immunotherapy, particularly immune checkpoint inhibitors (ICIs)(40). These ICIs efficiently release the brakes on the immune system by targeting important molecules such cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), PD-1, and its ligands PD-L1 and PD-L2. ICIs improve the capacity of immune cells, especially T lymphocytes, to identify and eliminate cancer cells by obstructing the communication between these proteins. With an overall response rate of 17%, early clinical studies demonstrated the efficacy of pembrolizumab, an anti-PD-1 monoclonal antibody, in treating patients with advanced cervical cancer(41). According to these research, pembrolizumab's safety profile is comparable to that of other cancer types. In patients with recurrent or metastatic squamous cervical carcinoma, other studies investigated the combination use of PD-1 and CTLA-4 receptor inhibitors, such as nivolumab and ipilimumab(42). According to these trials, both therapy groups had optimum response rates, and patients getting their first treatment showed increased effectiveness. Furthermore, when administered as monotherapy in patients with recurrent or metastatic cervical cancer after the failure of platinum-based chemotherapy, cadonilimab, a novel bispecific monoclonal antibody that targets both PD-1 and CTLA-4, has shown significant promise(43). Cadonilimab had an overall response rate (ORR) of 33% in a significant phase II clinical study; among patients whose tumors displayed PD-L1 positive, the ORR was significantly higher at 43.8%(44).

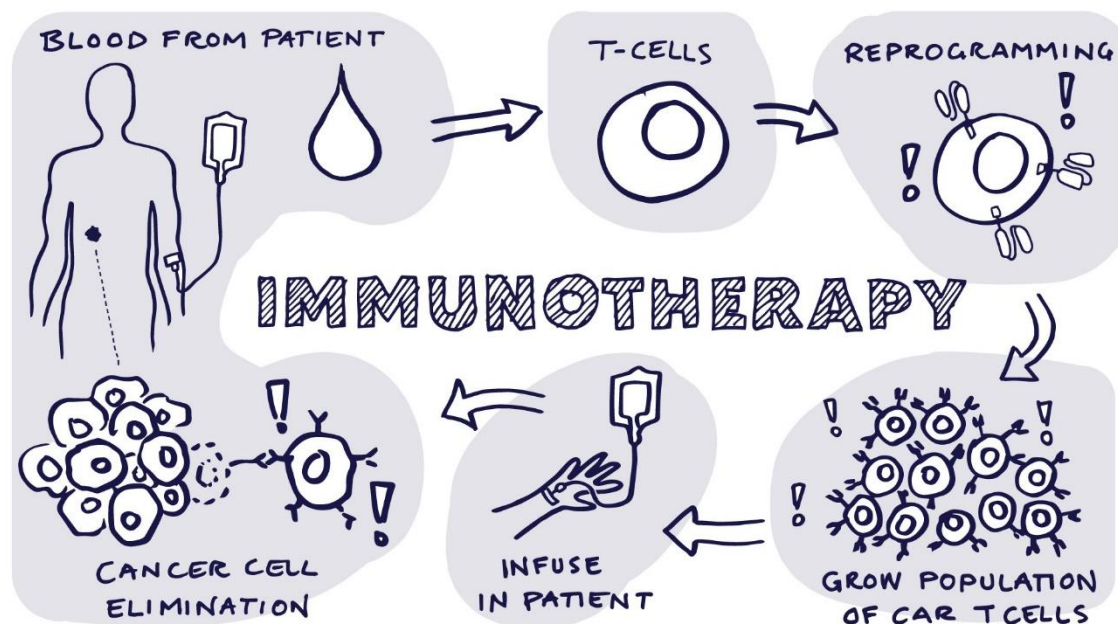


Figure 2 Immunotherapy

3.5. Targeted Therapy

Specialized medications that target certain molecules or pathways that contribute to the initiation and spread of disease are used in targeted treatment for cervical cancer. The goal of these therapies is to prevent cancer cells from growing while causing the least amount of damage to healthy, normal cells(44). Inhibitors of Vascular Endothelial Growth Factor (VEGF) and Epidermal Growth Factor Receptor (EGFR) are two important examples. These drugs have shown promising results in clinical trials, particularly when used in conjunction with more traditional treatments like chemotherapy or radiation therapy(43). For cervical cancer, targeted medicines provide a less harmful and more precise therapeutic alternative that may improve patient outcomes. By inhibiting the proteins that cancer cells make, these treatments stop the development and spread of cancer cells(42). Compared to conventional chemotherapies, these treatments are anticipated to be more successful and have fewer adverse effects because of their focused impact on cancer cells. In patients with advanced cervical cancer, a phase III clinical study evaluated the efficacy of combining non-platinum combination chemotherapy with bevacizumab, a monoclonal antibody that neutralizes VEGF(45). According to the experiment, bevacizumab increased response rates (48% against 36%) and overall survival (17.0 months versus 13.3 months). However, as compared to chemotherapy alone, bevacizumab significantly increased the incidence of gastrointestinal fistulas, thromboembolic events, and hypertension. Bevacizumab, paclitaxel, and cisplatin are now thought to be the new standard therapy for advanced and recurring cervical cancer(46).

4. FUTURE PROSPECTS IN CERVICAL CANCER MANAGEMENT

4.1. Therapeutic vaccine

Although preventative vaccinations increase humoral immunity, individuals who are already infected with high-risk HPV strains do not benefit therapeutically from them(47). Research on therapeutic HPV vaccines is still in its infancy, although they come in a variety of forms, such as whole-cell, peptide and protein, live vector, and nucleic acid-based vaccines. Since HPV E6 and E7 oncoproteins are found in HPV-infected cells and are essential for the development of cancer, the majority of these therapeutic vaccines are made to target them(48). In order to eliminate contaminated cells and halt the spread of malignancy, the main goal is to activate T cell responses against these proteins. By boosting immune responses against the HPV E6 and E7 proteins found in infected cells, these vaccines seek to eradicate the virus and stop the spread of the illness. Comparable to conventional lesion treatment techniques, MVA-E2, a top therapeutic vaccination, has shown up to 90% regression in individuals with high-grade cervical precancerous lesions. The absence of a control group to evaluate the lesion

regression rate naturally in the absence of therapy was a research constraint(49). Combination therapies that include both immunotherapy medications and therapeutic vaccinations are now being investigated as potential viable treatments for cervical cancer. One such instance is the ISA101 vaccination, which demonstrated a 33% response rate in a phase II research when administered in conjunction with the checkpoint inhibitor nivolumab. However, individuals with advanced cervical cancer did not exhibit this encouraging response, underscoring the need for more study and development(50). Although they are not yet as effective as proven treatments, therapeutic vaccinations have great promise as supportive medicines to reduce the risk of cancer recurrence and prevent intrusive procedures. Ongoing research keeps improving vaccination antigens and investigating the best combination treatment approaches in an effort to enhance results(51).

4.2. PARP Inhibitor

An essential enzyme for repairing damaged DNA is poly (adenosine diphosphate [ADP]-ribose) polymerase, especially PARP1. Cell death results from the blocking of this repair pathway by PARP inhibitors such as olaparib and veliparib, which are particularly harmful to cells that lack efficient homologous recombination repair(52). According to a case study, a woman with recurrent metastatic clear cell cervical carcinoma showed great promise when treated with olaparib alone. Over the course of 14 months, the patient showed no symptoms of illness development, demonstrating an extraordinary response to olaparib medication. Furthermore, a clinical study assessing veliparib in conjunction with cisplatin and paclitaxel as chemotherapeutic drugs demonstrated an overall survival time of 14.5 months and an objective response rate of 34%. Even with these encouraging outcomes, further clinical studies and trials are necessary to completely validate the long-term advantages and therapeutic efficiency of PARP inhibitors in the treatment of cervical cancer(53).

4.3. Antibody drug conjugate

An antibody-drug combination called tisotumab vedotin is made up of a human tissue factor antibody and an anti-microtubule agent. The transmembrane protein tissue factor, which is extensively expressed on the surface of cancer cells, is bound by this medication(54). After attaching itself, it is taken up by the cell and releases the anti-microtubule agent, which causes the structural elements of the cell to break down and ultimately results in cell death. In September 2021, the FDA approved tisotumab vedotin for the treatment of individuals with metastatic or recurrent cervical cancer.

4.4. RR Inhibitor

Because it makes it easier to convert nucleoside di- or triphosphates into their corresponding deoxynucleotides, ribonucleotide reductase (RR) is a crucial enzyme in DNA synthesis. Triapine and hydroxyurea are two examples of RR inhibitors that are being investigated and used to treat cervical cancer(55). Studies have shown the efficacy of radiation treatment in treating locally advanced cervical cancer when paired with either cisplatin alone or cisplatin, fluorouracil, and hydroxyurea. Preclinical research has shown promise for triapine, a more effective RR inhibitor, and preliminary clinical trials suggest that it may increase tumor sensitivity to radiation, especially when treating cervical cancer. Nevertheless, further research is required to confirm its efficacy in clinical situations.

4.5. Ongoing clinical trials

With their creative methods, current cervical cancer clinical trials are drastically changing future therapy plans. Research initiatives such as INTERLACE and KEYNOTE-A18 are spearheading attempts to evaluate the contribution of immune checkpoint inhibitors and induction chemotherapy to better treatment outcomes for cervical cancer that has spread locally. While KEYNOTE-A18 is assessing the addition of pembrolizumab to conventional chemotherapy, full data is still pending. INTERLACE's findings indicate that induction chemotherapy provides greater survival advantages than routine chemoradiotherapy(56). Trials like KEYNOTE-826 and BEATcc, which combine immune checkpoint inhibitors with chemotherapy and anti-angiogenic medicines, are concentrating on advanced cervical cancer and have shown encouraging increases in survival. A significant milestone has been reached with the recent approval of tisotumab vedotin as a second-line therapy for recurrent or metastatic cervical cancer. This medication and pembrolizumab are being thoroughly studied in a

number of studies with various treatment scenarios. Furthermore, a number of focused research are advancing our knowledge of how to treat cervical cancer. Vudalimab is an experimental medication being evaluated in the Phase 2 XmAb20717 study for advanced gynecologic and genitourinary malignancies, including cervical cancer(57). In order to determine the advantages of robotic technology in surgery, another important research is comparing the survival results of open radical hysterectomy with robotic-assisted laparoscopic surgery for early-stage cervical cancer. Furthermore, the ACCESS Trial is incorporating cervical cancer screening and treatment into Nigeria's current HIV care programs, exploring different approaches to improve patient outcomes and increase access in underprivileged regions. In nations like India, this concept of incorporating cervical cancer treatment within HIV programs has the potential to maximize services and enhance results, particularly for women from underserved regions, by providing an affordable and easily accessible healthcare option.

5. CONCLUSION

In summary, cervical cancer continues to be a serious worldwide health issue. Advanced therapeutics including immunotherapy, targeted treatments, and gene-based techniques are emerging as viable alternatives, despite the limits of current treatment choices. Patient outcomes might be greatly improved by implementing these cutting-edge techniques into standard therapeutic practice. It will need ongoing research and teamwork to improve treatment plans and effectively convert these new treatments into affordable and efficient cervical cancer treatment options.

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