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The role of immunotherapy in the treatment of advanced cervical cancer: New guidelines and future perspectives

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ABSTRACT

Cervical cancer is one of the most common malignancies globally, particularly prevalent in low- and middle-income countries, and is the second most prevalent cancer-related cause of death. Despite the improvement in screening and preventive efficacy of the HPV vaccines, the majority of these cancers are diagnosed at a late stage where traditional therapies like chemotherapy and radiotherapy are of minimal benefit with disappointing long-term survival. In the past few years, immunotherapy has emerged as a breakthrough approach in oncology, offering new treatment options for recurrent or advanced cervical cancer. This narrative review discusses the current place and future directions of immunotherapy in advanced cervical cancer. The review addresses key mechanisms of tumor immune escape including HPV-mediated expression of viral oncoproteins E6 and E7, PD-L1 overexpression, and the immunosuppressive tumor microenvironment. The review criticizes several immunotherapeutic modalities such as immune checkpoint inhibitors (e.g., pembrolizumab, nivolumab), adoptive cell therapies (CAR-T, TILs), therapeutic vaccines, and monoclonal antibodies. Furthermore, it highlights the rationale and clinical benefit of combining immunotherapy with chemotherapy, radiotherapy, and targeted agents such as bevacizumab, as in trials such as KEYNOTE-826. While immunotherapy is a paradigm change in the treatment of cervical cancer, there are challenges. These are lack of access, cost of therapy, immune resistance, and need for predictive biomarkers. These limitations will be overcome by research and global health policy to make immunotherapy a just and effective option for all patients with cervical cancer.

Keywords: cervical cancer, immunotherapy, HPV, checkpoint inhibitors, PD-1, clinical guidelines

1. INTRODUCTION

Cervical cancer is the leading cancer of the reproductive organs in the world and the fourth primary cause of cancer death in women. More than 70% of cervical cancer deaths occur in low- and middle-income countries, where this disease ranks

second among women in both incidence and mortality (Grau-Bejar et al., 2023). Despite overall awareness of its viral etiology and availability of HPV vaccination and routine screening programs, a significant proportion of cases are still diagnosed late. In these cases, the disease has a tendency to progress aggressively and is noted for having limited therapy alternatives and a general poor prognosis. Standard treatments such as chemotherapy and radiotherapy, while effective at the early stages, demonstrate diminishing effectiveness once the disease has metastasized or progressed after initial treatment (Bestvina et al., 2016).

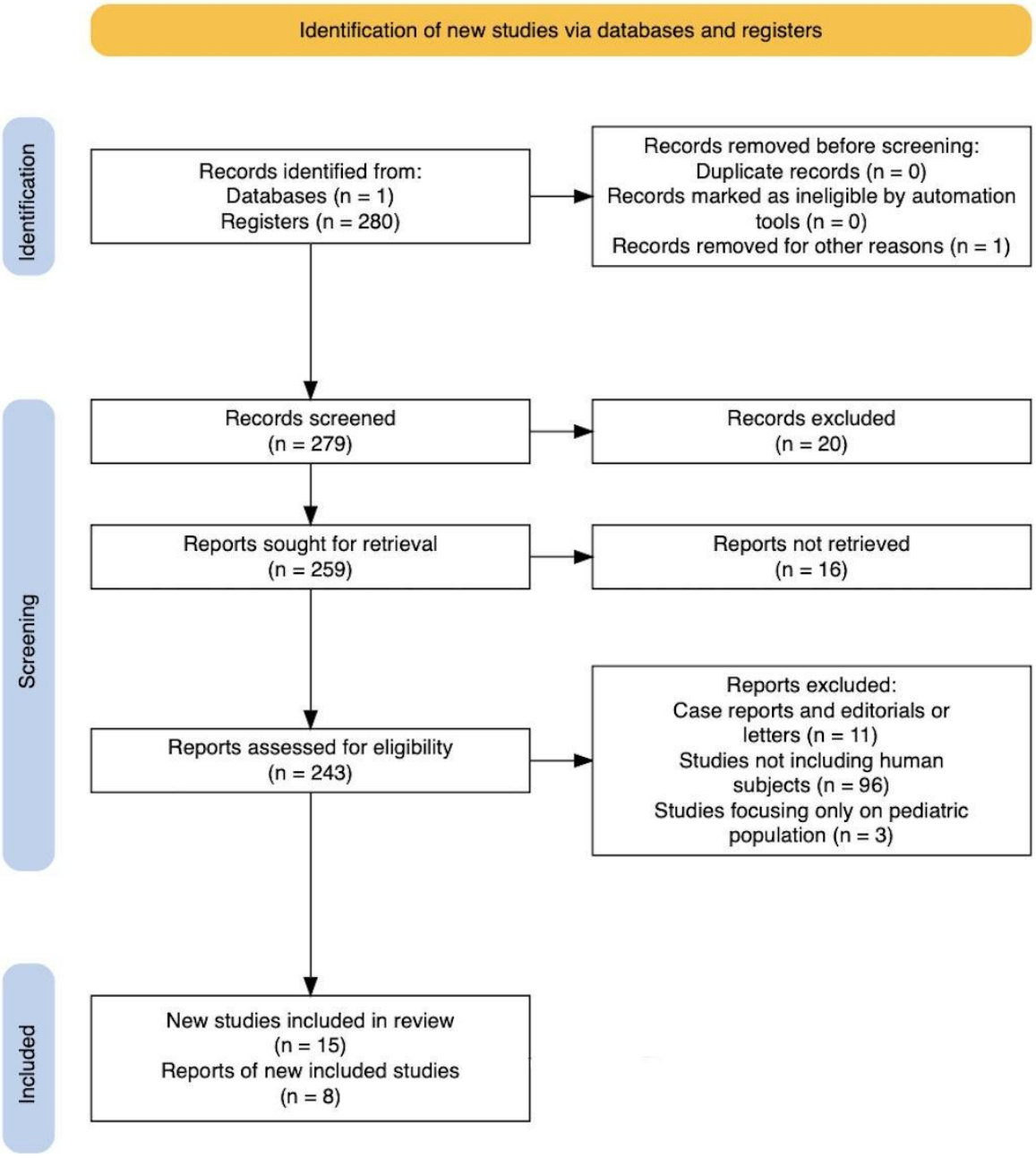

Figure 1. PRISMA Flow Chart.

Over time, advanced cervical cancer has been challenging to treat because of the aggressive nature of the disease and its ineffectiveness. Immunotherapy has recently appeared as a novel and exciting treatment option for cancer. Immunotherapy is also providing more durable and customized treatment results by targeting particular immune checkpoints and enhancing the body's

defenses against tumor cells (Song et al., 2020). Drugs such as PD-1 and PD-L1 inhibitors have demonstrated encouraging results in many types of solid tumors, including cervical cancer, to offer new hope for patients who previously had few alternatives (Shiravand et al., 2022).

The objective of this paper is to explore the evolving role of immunotherapy as a treatment for advanced cervical cancer. It provides an overview of current clinical recommendations, summarize evidence for immune checkpoint inhibitors, and discuss emerging strategies and future perspectives in this quickly developing therapeutic area. Awareness of the inclusion of immunotherapy into routine treatment regimens could significantly impact survival and quality of life in advanced disease stage diagnosed patients.

2. REVIEW METHODS

This article is a narrative review on the use of immunotherapy in advanced cervical cancer treatment. A high-impact scientific literature was searched through PubMed. Keywords included here were "cervical cancer","immunotherapy", "checkpoint inhibitors" and "PD-1"to search for relevant articles. A search was conducted using studies published between January 2013 and May 2025. Some studies were reviewed to evaluate ongoing treatment modalities, clinical outcomes, and future research directions (figure 1).

3. RESULTS AND DISCUSSION

3.1 Cervical Cancer risk factors

Cervical cancer is strongly associated with infection by oncogenic types of human papillomavirus (HPV), primarily HPV-16 and HPV-18. Although HPV infection is a necessity, it is, by itself, insufficient to result in cancer. Several other risk factors are implicated in the pathway from infection to malignancy (Okunade, 2020).

Among the most potent cofactors are precocious initiation of sexual activity and sexual partners, which increase risk of acquisition and maintenance of HPV infection. Cigarette smoking is also a well-established risk factor, as it undermines local immune defense and facilitates oncogenic transformation of cervical epithelial cells. Extended use of oral contraceptives (beyond five years) has also been associated with an increase in risk by a small amount (El-Zein et al., 2019).

Immunosuppression, especially in women with HIV, significantly enhances the risk of progression of lesions to high-grade lesions and cancer. Other risk factors include low socioeconomic status, limited access to medical care and screening, multiparity (having given birth to three or more children), and co-infection with other STDs (e.g., chlamydia, herpes simplex virus type 2) (Bhatla et al., 2013).

An extensive understanding of all these risk factors is not only required for prevention, but also for identification of high-risk groups that will most likely respond to early intervention and immunization strategies.

3.2 The Role of HPV in the Pathogenesis of Cervical Cancer

Human papillomavirus (HPV) plays a significant role significant role in the causation of cervical cancer and is also called its primary etiological agent. High-risk HPV types are a group 1 carcinogen and include types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 66, which occur in over 99% of cervical cancers (Okunade, 2020). The virus is sexually transmitted and the infection is transient in most people since the immune system clears the virus within one to two years (Hewavisenti et al., 2023).

However, the infection recurs in some women, which significantly increases the risk of the development of cervical intraepithelial neoplasia (CIN) and eventually invasive cervical carcinoma. The oncogenic potential of high-risk types of HPV is the result of the expression of viral oncoproteins E6 and E7, which inhibit tumor suppressor proteins such as p53 and retinoblastoma protein (Zheng et al., 2016). This disruption leads to uncontrolled cell growth, genomic instability, and accumulation of mutations that drive the progression to malignancy

Understanding the molecular mechanisms of HPV-induced carcinogenesis is crucial for planning preventive interventions, such as vaccination and screening for precancerous lesions early on.

3.3 Mechanisms of Immune Evasion by Tumor Cells

Cervical cancer cells, particularly those transformed by high-risk HPV infection, utilize multiple mechanisms to evade immune detection and destruction. A central strategy involves the expression of viral oncoproteins E6 and E7. The E6 protein promotes carcinogenesis by binding to the tumor suppressor p53 protein and inducing its degradation. This blocks the cell's ability to halt the cell cycle and initiate programmed cell death (apoptosis). The E7 protein binds to the retinoblastoma protein simultaneously, blocking its suppression of the E2F family of transcription factors. Therefore, E2F is freed and promotes genes that allow for the unrestricted

growth of cells. At the same time, loss of p53 and Rb function causes genetic instability, continuous cell proliferation, and avoidance of apoptosis—key steps in cervical cancer formation (Dey and Agrawal, 2025).

Another key immune evasion tactic is the downregulation of MHC class I molecules, reducing antigen presentation to cytotoxic T lymphocytes (Cornel et al., 2020). In addition, tumor cells frequently upregulate immune checkpoint ligands, most notably PD-L1, which binds to PD-1 receptors on T cells and leads to their functional exhaustion or energy. Therapies targeting the PD-1/PD-L1 pathway have revolutionized cancer treatment, demonstrating significant effectiveness against various cancer types. Immune checkpoint inhibitors (ICIs) belong to the group of therapeutic agents that interfere with immune checkpoint pathways, thereby restoring the immune system's ability to recognize and eliminate cancer cells. A key group within this category are monoclonal antibodies (mAbs), which are engineered proteins designed to specifically bind to targets on cancer cells or immune cells—most notably proteins such as PD-1 and PD-L1. By blocking these pathways, ICIs reinvigorate the activity of cytotoxic T cells, enhancing their ability to mount a sustained anti-tumor response across various types of cancer (Parvez et al., 2023).

3.4 Immunotherapy: Mechanisms of Action

3.4.1 Immune checkpoint inhibitors

Recent studies in patients with advanced cervical cancer have shown that suppresing the PD-1/PD-L1 pathway can effectively restore the activity of exhausted cytotoxic T lymphocytes (CTLs), thereby enhancing the immune system's ability to target and eliminate cancer cells (Shiravand et al., 2022). Cervical cancer, particularly HPV-related subtypes, often exhibits high levels of PD-L1 expression on tumor and immune cells within the tumor microenvironment. This expression allows the tumor to evade immune destruction by suppressing T-cell activation through the PD-1 receptor.

Immune checkpoint inhibitors, such as pembrolizumab and nivolumab, are monoclonal antibodies that block this interaction, enabling reactivation of T-cell responses. By doing so, they help overcome the immunosuppressive environment created by HPV-driven oncogenesis. Clinical evidence, such as results from the KEYNOTE-826 trial, has shown that combining pembrolizumab with chemotherapy improves overall survival and in patients with persistent, recurrent, or metastatic cervical cancer (Monk et al., 2023).

This approach represents a major advancement in the treatment of cervical cancer, particularly for patients who have limited options after failure of conventional therapies. The ability to reawaken T cells and restore immune surveillance offers new hope for durable disease control in this aggressive malignancy.

3.4.2 Adoptive Immunotherapy (CAR-T and TILs)

Adoptive immunotherapy involves the transfer of autologous or gene-engineered immune cells to enhance the body's ability to recognize and destroy cancer cells. Chimeric antigen receptor T cells (CAR-T) and tumor-infiltrating lymphocytes (TILs) are two of the promising modalities of adoptive cell therapy in cancer.

CAR-T cell therapy is the genetic engineering of a patient's T cells to introduce artificial receptors (CARs) that are specific for recognizing tumor-associated antigens (Uscanga-Palomeque et al., 2023). This has been overwhelmingly effective in hematologic malignancies, and studies are ongoing to assess its promise in solid tumors, such as cervical cancer. However, challenges including antigen heterogeneity, limited tumor infiltration, and the immunosuppressive state of the tumor microenvironment need to be addressed.

TIL therapy involves isolating the lymphocytes directly from the patient's tumor, culturing them outside the body, and reinfusing them into the patient after lymphodepletion (Zhao et al., 2022). TILs intrinsically have the ability to recognize tumor-specific antigens, particularly in virus-related cancers like HPV-positive cervical cancer (Tang et al., 2021). Early-stage clinical trial results were encouraging in patients with refractory metastatic cervical cancer.

Adoptive cell therapies offer a very specific and individualized means of cancer treatment with immense potential for their use in the future in cervical cancer management.

3.4.3 Cancer Vaccines and Monoclonal Antibody Therapy in Cervical Cancer

In the context of cervical cancer, cancer vaccines and monoclonal antibody therapy represent two innovative approaches in immuno-oncology that complement existing treatment modalities. Unlike traditional vaccines aimed at preventing infection, therapeutic cancer vaccines are designed to stimulate the immune system to recognize and destroy tumor cells by targeting tumor-specific or tumor-associated antigens (Kaczmarek et al., 2023).

In HPV-related cervical cancer, the presence of viral oncoproteins E6 and E7 makes this disease particularly suitable for vaccine-based strategies. These viral proteins are consistently expressed in malignant cells but absent in normal tissues, making them ideal immunological targets. Vaccines under investigation—such as peptide-based, DNA-based, and dendritic cell vaccines—seek to enhance T-cell responses against HPV-driven tumors (Liu et al., 2024). Although therapeutic vaccines are still largely in the experimental stage, early-phase trials have shown immunogenic activity and potential clinical benefit, especially when combined with other immunotherapeutic agents.

Monoclonal antibodies (mAbs), on the other hand, are lab-engineered proteins that bind to specific antigens on cancer or immune cells (Aboul-Ella et al., 2024).In cervical cancer, mAbs targeting PD-1/PD-L1 (e.g., pembrolizumab) are already approved for clinical use in patients with advanced disease (Huang et al., 2022). Other monoclonal antibodies under study include those directed against VEGF (vascular endothelial growth factor), aiming to disrupt tumor angiogenesis and improve immune cell infiltration (Mahaki et al., 2025). The development of bispecific antibodies, which simultaneously bind tumor antigens and activate T cells, is also a promising area of research.

Together, vaccines and monoclonal antibodies represent highly specific and targeted approaches that hold potential to improve immune-mediated tumor control, especially when integrated into multimodal treatment strategies.

3.4.4 Combining Immunotherapy with Chemotherapy, Radiotherapy, and Targeted Therapies

While immunotherapy has shown great promise as a standalone approach, recent advances emphasize the potential benefits of combining immunotherapy with other conventional treatments, such as chemotherapy, radiotherapy, and targeted therapies, to achieve synergistic effects (Garg et al., 2024).

Chemotherapy, traditionally known for its cytotoxic effects, can also modulate the immune system in favorable ways. Certain chemotherapeutic agents increase the release of tumor antigens and reduce immunosuppressive cell populations within the tumor microenvironment. When combined with immune checkpoint inhibitors (ICIs), chemotherapy may enhance T-cell infiltration and improve the efficacy of immunotherapy. For example, the combination of pembrolizumab and platinum-based chemotherapy has become a standard option in the treatment of advanced cervical cancer following the results of the KEYNOTE-826 trial (Monk et al., 2023).

Radiotherapy can also act as an immunological primer by inducing immunogenic cell death and promoting the presentation of tumor antigens. This process, known as the abscopal effect, may convert an irradiated tumor into a site of immune activation, amplifying the systemic effects of ICIs.

Moreover, the integration of targeted therapies—such as anti-angiogenic agents like bevacizumab—with immunotherapy is being explored to overcome resistance mechanisms and enhance immune cell access to the tumor (Song et al., 2020). By normalizing the tumor vasculature and reducing hypoxia, these agents can improve the efficacy of immune-based treatments.

Overall, combination strategies reflect a trend toward personalized and multimodal cancer treatment, where immunotherapy is not viewed in isolation but as one facet of an integrated treatment plan that is tailored to individual tumor biology and immune profiles.

Table 1. Mechanisms of action of immunotherapy in Cervical Cancer

Immunotherapy type	Mechanism of action	Clinical notes
Immune Checkpoint Inhibitors	Block PD-1/PD-L1 interaction to restore T-cell activity and promote anti-tumor response (Shiravand et al., 2022).	Pembrolizumab + chemo improves survival in advanced cervical cancer (KEYNOTE-826).
CAR-T Cell Therapy	Genetically engineered T cells with tumor-specific CARs recognize and kill cancer cells (Uscanga-Palomeque et al., 2023).	Effective in hematologic cancers; under investigation in cervical cancer.
Tumor-Infiltrating Lymphocytes (TILs)	Autologous T cells extracted from tumor, expanded ex vivo, and reinfused to enhance immune attack (Zhao et al., 2022).	Promising in HPV-positive cases with metastatic disease.

Therapeutic Cancer Vaccines	Stimulate immune system to target tumor-specific HPV antigens (e.g., E6/E7) and boost T-cell responses (Liu et al., 2024).	Still experimental; potential benefit seen in early trials when combined with other therapies.
Monoclonal Antibody Therapy	Lab-made antibodies target tumor antigens (e.g., PD-1, VEGF) to enhance immune surveillance (Aboul-Ella et al., 2024).	Approved therapies (e.g., pembrolizumab); bispecific antibodies under development.
Combination with Chemotherapy	Enhances tumor antigen release and reduces suppressive cells, synergizing with immune checkpoint inhibitors (Monk et al., 2023).	Standard regimen now includes checkpoint blockade plus chemo.
Combination with Radiotherapy	Induces immunogenic cell death, promoting antigen presentation and systemic immune activation (Garg et al., 2024).	Explores abscopal effect to amplify systemic immune responses.
Combination with Targeted Therapies	Normalizes tumor vasculature and improves immune infiltration to increase therapy effectiveness (Song et al., 2020).	Enhances immunotherapy by overcoming hypoxia and resistance mechanisms.

3.5. Limitations in the clinical application of immunotherapy

In spite of the increasing potential of immunotherapy for the cure of advanced cervical cancer, some major obstacles and drawbacks persist to limit its extensive use and long-term efficiency.

The most critical issue is cost and accessibility, particularly in low- and middle-income countries, where cervical cancer is more burdensome. Immune checkpoint inhibitors and other newer drugs are costly, and weak healthcare infrastructure further restricts access to these. This disparity creates an international disparity in cancer therapy, and it aggravates disparities in survival and outcome.

The second major problem is primary or secondary resistance to immunotherapy. While sustained responses are observed in some individuals, others do not respond or worsen with therapy. Cancersmay adapt by upregulating other immune checkpoint mechanisms, modifying antigen presentation, or modifying their microenvironment to suppress immune function. Such immune escape mechanisms pose a major challenge to reproducible and durable responses.

Furthermore, the area still has no solid predictive biomarkers to determine which patients will receive the most benefit from immunotherapy. PD-L1 expression is used most often, but this isn't always reflective of outcomes.

Finally, there are also ethical and practical challenges in embracing new therapies. Among these are problems of equitable use of resources, informed consent in vulnerable populations, and the complexities of incorporating new therapies into formal care frameworks. Overcoming these challenges is central to fully realizing the potential of immunotherapy in cervical cancer therapy and bringing it within reach of all patients, regardless of geography or socioeconomic status.

4. CONCLUSIONS

Immunotherapy has been a new approach to the treatment of advanced cervical cancer, bringing new hope to patients with poor prognosis and few alternatives. The intimate link between HPV infection and cervical carcinogenesis offers a unique opportunity for immunology-based treatment because viral oncogenes such as E6 and E7 are natural targets for immune attack. For this purpose, immune checkpoint inhibitors, and indeed PD-1/PD-L1 inhibitors like pembrolizumab, have been shown to be successful in the clinic and are being introduced into standard treatment regimens in select patient populations. The new field of immunotherapy also includes adoptive cell therapies such as CAR-T cells and TILs, which leverage and expand the body's own immune resources to recognize and kill cancer cells. Similarly, therapeutic vaccines against HPV-associated antigens, monoclonal antibodies, and bispecific

constructs are new and highly specific strategies under active investigation. These new strategies are trying to circumvent tumor immune evasion and to provide better control of long-term disease. Yet, there are still significant challenges to be addressed. Therapeutic advances continue to be limited by the expense of immunotherapy and unequal healthcare infrastructure, especially in low- and middle-income countries where cervical cancer is most prevalent. Resistance mechanisms, lack of robust predictive biomarkers, and ethical concerns relating to implementation and equity must be surmounted through ongoing research, policy development, and global collaboration. While immunotherapy is not yet poised to offer a cure for all metastatic cervical cancer patients, it has altered treatment possibilities and paved the way for a more individualized, effective, and hopeful future. Increased clinical investigation and greater access will be essential to maximize its best in many different groups worldwide.

Author's Contributions

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Formal analysis: Sara Hassan
Resources, data curation: Kamil Hassan
Investigation: Sara Hassan, Szymon Bienia
Writing – original draft: Sara Hassan, Szymon Bienia
Writing – review & editing: Sara Hassan, Szymon Bienia
All authors have read and agreed with the final, published version of the manuscript.

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Informed consent

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Ethical approval

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Conflict of interest

The authors declare that there is no conflict of interest.

Data and materials availability

All data associated with this study will be available based on the reasonable request to corresponding author.

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