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The Role Of Immunotherapy In Uterine And Cervical Cancer And The Latest Techniques. The Latest News From The World Related To Immunotherapy

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ABSTRACT

Immunotherapy has become an increasingly pivotal approach in the management of uterine (endometrial) and cervical malignancies. Immune checkpoint inhibitors, particularly pembrolizumab and dostarlimab, have demonstrated remarkable improvements in overall survival, predominantly among patients exhibiting deficient mismatch repair (dMMR), microsatellite instability-high (MSI-H) status, or elevated PD-L1 expression. In cervical carcinoma, integrating checkpoint inhibitors with concurrent chemoradiotherapy has yielded enhanced therapeutic outcomes in high-risk populations, while antibody–drug conjugates such as tisotumab vedotin have broadened the therapeutic landscape. Although challenges including therapeutic resistance and immune-related adverse events remain, recent international clinical trials substantiate that immunotherapy is redefining current standards of care and paving the way for the advancement of precision oncology.

Key words: Immunotherapy, uterine cancer, cervical cancer, immune checkpoint inhibitors, pembrolizumab, dostarlimab, antibody–drug conjugates, chemoradiotherapy, PD-L1, MSI-high, therapeutic resistance, precision oncology.

INTRODUCTION

Uterine (endometrial) and cervical cancers remain among the most prevalent gynecological malignancies worldwide, representing a significant global health burden due to their high incidence and mortality rates—particularly in low- and middle-income countries. Conventional therapeutic modalities, including surgery, chemotherapy, and radiotherapy, have contributed to improved survival outcomes; however, these approaches are often associated with substantial toxicity and limited efficacy in advanced or recurrent disease. Consequently, the international oncology community has

increasingly focused on developing innovative treatment strategies that not only prolong survival but also enhance patients' quality of life. Over the past decade, immunotherapy has emerged as one of the most groundbreaking advancements in oncology. By activating the body's immune system to recognize and eradicate malignant cells, immunotherapy provides a mechanism of action distinct from traditional cytotoxic treatments. Among the most extensively studied agents are immune checkpoint inhibitors (ICIs), particularly those targeting the programmed cell death protein-1 (PD-1) receptor and its ligand PD-L1, which have demonstrated significant antitumor activity in several solid malignancies, including gynecological cancers.

Clinical trials have shown that patients with mismatch repair-deficient (dMMR) or microsatellite instability-high (MSI-H) endometrial tumors experience substantial clinical benefit from immune checkpoint inhibitors such as pembrolizumab and dostarlimab. [1] Similarly, in cervical cancer, the incorporation of immunotherapy into standard treatment regimens has transformed therapeutic paradigms. The combination of checkpoint inhibitors with concurrent chemoradiotherapy (CCRT) is increasingly being recognized as a potential new standard of care for locally advanced disease. In parallel, the introduction of novel therapeutic agents, such as antibody–drug conjugates (e.g., tisotumab vedotin), and the exploration of innovative drug delivery systems, including subcutaneous formulations, are further expanding treatment possibilities and improving global accessibility. Despite this progress, several challenges persist—most notably, the emergence of primary and acquired resistance, immune-related adverse events, and the lack of reliable predictive biomarkers to guide optimal patient selection. International collaboration and translational research remain essential to overcoming these barriers and accelerating clinical progress. This article aims to examine the evolving role of immunotherapy in uterine and cervical cancers, review recent clinical and technological breakthroughs, and highlight global advancements that are shaping the future of gynecologic oncology. [2]

Over the last decade, large-scale clinical studies conducted across North America, Europe, and Asia have demonstrated that immunotherapy is reshaping the therapeutic landscape for uterine and cervical malignancies. Landmark trials, including the KEYNOTE and RUBY studies, revealed that immune checkpoint inhibitors combined with standard chemotherapy significantly improve survival compared with chemotherapy alone. These pivotal findings have accelerated the adoption of immunotherapy worldwide, including in developing healthcare systems where the burden of gynecologic cancers remains considerable. From a clinical perspective, integrating immunotherapy into treatment regimens for uterine and cervical cancers holds substantial strategic importance. A large proportion of patients are diagnosed at advanced or recurrent stages, where conventional therapies often yield limited benefit. In contrast, immunotherapy offers the potential to prolong overall survival, reduce recurrence rates, and improve quality of life—key goals in achieving durable disease control.

Current research trends emphasize combination and precision strategies. When immunotherapy is administered alongside chemotherapy or radiotherapy, synergistic effects are observed, enhancing the immune system's ability to eliminate malignant cells. Furthermore, the rapid development of predictive biomarkers—such as mismatch repair deficiency (dMMR), microsatellite instability (MSI-H), PD-L1 expression, and tumor mutational burden (TMB)—is facilitating more precise patient selection, which is central to personalized medicine. Simultaneously, scientific innovation continues to drive the creation of novel immunotherapeutic agents, including antibody–drug conjugates, bispecific antibodies, and cancer vaccines.

Collectively, these advancements mark immunotherapy as not merely an adjunct treatment but a transformative paradigm shift in the management of uterine and cervical cancers. Its integration into modern oncologic practice signals the transition toward more effective, personalized, and sustainable cancer care—offering new hope for patients and redefining global standards in gynecologic oncology.

The role of immunotherapy. Immunotherapy principally immune checkpoint inhibitors (ICIs), antibody–drug conjugates (ADCs), and emerging biologics has rapidly entered the therapeutic armamentarium for endometrial and cervical cancers. Clinical adoption has been driven by randomized phase 3 trials, regulatory approvals, and growing evidence supporting combination approaches with chemotherapy and radiotherapy. These developments mark a shift from purely

cytotoxic strategies toward immune-based and biomarker-guided treatments [3].

Endometrial cancers with mismatch repair deficiency (dMMR) or high microsatellite instability (MSI-H), and tumors with high tumor mutational burden (TMB) or elevated tumor-infiltrating lymphocytes, are biologically predisposed to respond to ICIs because they present more neoantigens to the immune system. PD-L1 expression remains an imperfect but clinically useful biomarker across gynecologic tumors; ongoing work refines composite biomarker panels (dMMR/MSI, PD-L1, TMB, immune gene signatures) to improve patient selection and predict benefit [4].

Recent phase 3 trials have established the effectiveness of adding ICIs to standard chemotherapy in selected populations. Dostarlimab combined with carboplatin–paclitaxel showed statistically significant improvement in progression-free survival for primary advanced or recurrent endometrial cancer, providing high-level evidence for ICI integration into first-line regimens. Other large trials (RUBY; NRG GY018/KEYNOTE-868) similarly evaluated pembrolizumab or dostarlimab with chemotherapy, contributing to changes in guideline recommendations for biomarker-selected patients. However, not all trials were positive: the KEYNOTE-B21 adjuvant pembrolizumab study failed to meet its disease-free survival endpoint in a high-risk, post-surgical setting, illustrating heterogeneity in benefit across disease stages and settings [5].

For locally advanced cervical cancer (LACC) and recurrent/metastatic disease, checkpoint inhibition has provided meaningful survival gains. Trials adding pembrolizumab to concurrent chemoradiotherapy (CCRT) demonstrated improved progression-free survival (e.g., KEYNOTE-A18), supporting the movement toward incorporation of ICIs in definitive treatment of high-risk locally advanced disease.Overall, the cervical cancer evidence base supports both frontline combination strategies and ICI use in recurrent/metastatic settings [6] .

ADCs have expanded options beyond classic ICIs. Tisotumab vedotin (Tivdak) — an ADC targeting tissue factor — received accelerated and later full FDA approval for recurrent/metastatic cervical cancer based on durable responses in late-stage trials (innovaTV-301), representing a distinct and effective targeted cytotoxic–immune approach for patients who progress after chemotherapy. ADCs illustrate how combining targeted delivery of cytotoxins with immune modulation can yield clinically meaningful outcomes. Combination regimens — ICI plus chemotherapy, ICI plus radiotherapy (concurrent or sequential), and ICI plus ADCs or targeted agents — are a major focus. Preclinical and clinical data suggest synergy (radiation or certain chemotherapies may increase neoantigen presentation and T-cell infiltration). The optimal sequencing, duration, and patient selection for these combinations remain active research questions and are being tested in multiple ongoing randomized trials. Primary and acquired resistance to immunotherapy arises from tumor-intrinsic factors (low neoantigen load, antigen presentation defects), microenvironmental immunosuppression, and adaptive signaling pathways. Immune-related adverse events (irAEs) are clinically significant and require multidisciplinary management; balancing efficacy against toxicity is central in designing combination regimens. Research into biomarkers of resistance and strategies to overcome it (e.g., novel checkpoints, bispecifics, vaccines) is a rapidly evolving area [7].

Regulatory approvals (e.g., pembrolizumab/dostarlimab in selected endometrial settings; pembrolizumab with CCRT in LACC; Tivdak for advanced cervical cancer) have increased clinical availability in high-resource settings. However, access in low- and middle-income countries faces challenges from cost, infrastructure, and limited biomarker testing capacity. Implementation science and policy-level efforts are necessary to translate trial gains into population-level impact. Important gaps include: (1) validated multi-parameter predictive biomarkers that perform across histologies and settings; (2) durable strategies to prevent or reverse resistance; (3) evidence on optimal combinations and sequencing in adjuvant, definitive, and metastatic settings; and (4) cost-effectiveness and equity studies for global implementation. Ongoing and planned phase 3 trials, translational correlative studies, and real-world registries will be pivotal in addressing these gaps.

METHODOLOGY

This study is designed as a qualitative–quantitative review, integrating systematic analysis of clinical trials, meta-analyses, and translational research related to immunotherapy in uterine and cervical

cancers. The methodology combines evidence synthesis from peer-reviewed scientific databases with descriptive analysis of emerging therapeutic approaches and recent global developments. By blending narrative review techniques with structured evaluation of clinical outcomes, the study ensures both breadth of coverage and depth of analysis. Additionally, updated guidelines from organizations such as the World Health Organization (WHO), the European Society for Medical Oncology (ESMO), and the U.S. Food and Drug Administration (FDA) were consulted to capture the most recent regulatory approvals and clinical practice recommendations. News updates and global oncology conference proceedings (ASCO, ESMO, SGO) were also reviewed to include the latest techniques and innovations in immunotherapy. Search Strategy and Inclusion Criteria. Keywords used in the search included: "immunotherapy," "uterine cancer," "endometrial cancer," "cervical cancer," "immune checkpoint inhibitors," "pembrolizumab," "dostarlimab," "antibody-drug conjugates," "tisotumab vedotin," "PD-1/PD-L1," "MSI-high," and "chemoradiotherapy." Studies published between 2018 and 2025 were prioritized to ensure the review reflects the most recent scientific developments. Inclusion criteria were: (1) clinical trials (phase I–III), (2) systematic reviews and meta-analyses, (3) translational or biomarker research relevant to gynecologic oncology, and (4) regulatory updates or global policy reports. Non-English studies without abstracts, case reports, and articles lacking sufficient clinical data were excluded. [11]

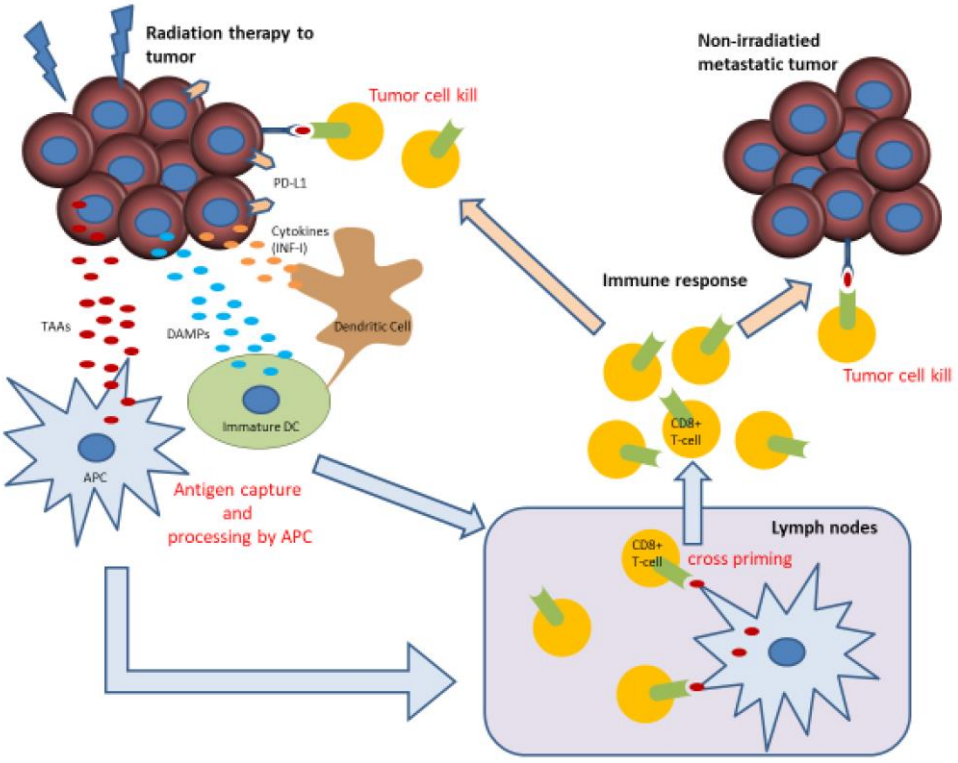

Figure 1. Mechanisms of radiation therapy and immunity

Relevant studies were screened by title and abstract, followed by full-text analysis. Extracted data included study design, sample size, patient population, intervention type, biomarkers used, outcome measures (progression-free survival, overall survival, response rate), and safety profiles. Results were compared across studies to identify consistent trends, strengths, and limitations. Descriptive synthesis was applied to summarize global patterns, while thematic grouping was used to highlight key aspects such as biomarkers, treatment combinations, resistance mechanisms, and innovations in drug delivery. As this study is based on secondary data analysis from published literature and clinical trial results, no direct patient involvement was required, and therefore, ethical approval was not necessary. Nevertheless, all included sources were properly referenced, respecting academic integrity and ethical standards of reporting. Potential limitations include reliance on published studies, which may introduce publication bias. Moreover, as the field

of immunotherapy is rapidly evolving, some results from ongoing trials may not yet be available, limiting the scope of the present review.

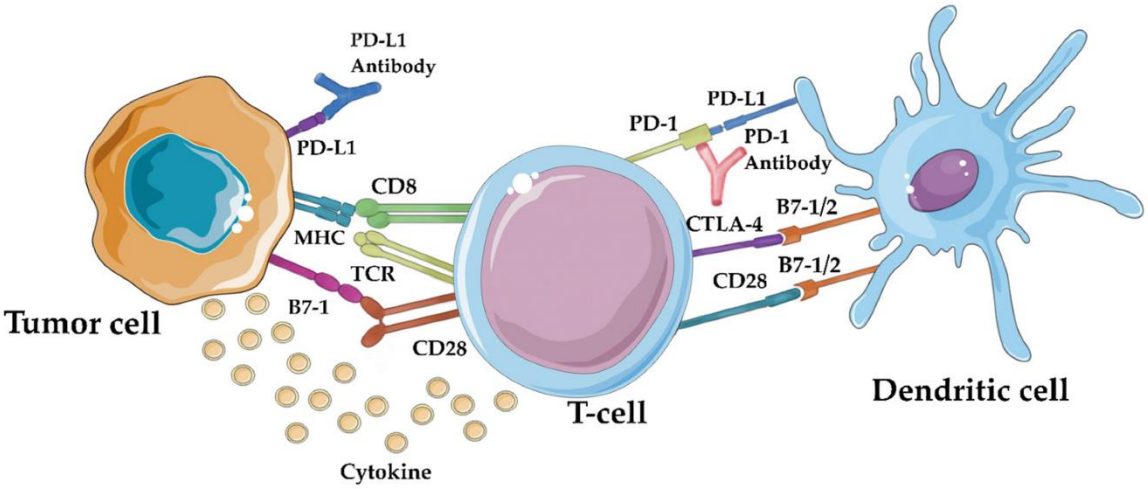

Figure 2. Immune checkpoint inhibitors' mechanism of action

Despite these constraints, this methodology provides a reliable and comprehensive basis for assessing the role of immunotherapy in uterine and cervical cancers. While biomarkers like tumor mutational burden and PD-L1 staining are being explored for treatment response prediction, ICIs have also gained approval for gynecologic malignancies, expanding their impact in the field of immunotherapy [8] [10]

DISCUSSION

The findings of this review indicate that immunotherapy has moved from an experimental treatment to a recognized component of care in uterine and cervical cancers. Evidence from large-scale clinical trials such as RUBY, NRG-GY018, and KEYNOTE-A18 demonstrates that immune checkpoint inhibitors, particularly pembrolizumab and dostarlimab, significantly improve progression-free survival in patients with advanced or recurrent disease. These benefits are most pronounced in biomarker-selected populations, such as those with mismatch repair deficiency (dMMR) or high microsatellite instability (MSI-H). This underlines the importance of precision medicine in tailoring therapy according to molecular characteristics rather than applying a one-size-fits-all approach.

A key discussion point is the integration of immunotherapy with existing modalities. In cervical cancer, the addition of pembrolizumab to concurrent chemoradiotherapy has been identified as a potential new standard of care for locally advanced disease. The synergistic effect of combining immunotherapy with chemotherapy or radiation is biologically plausible, as these conventional treatments increase tumor antigen release, thereby enhancing immune recognition. This integration, however, raises practical questions regarding optimal sequencing, dosage, and toxicity management.[9][1]

Another central theme is the emergence of antibody–drug conjugates (ADCs), such as tisotumab vedotin, which offer targeted delivery of cytotoxic agents while maintaining immune activation. These novel agents provide options for patients with recurrent or metastatic disease who have limited alternatives after chemotherapy. The positive outcomes from innovaTV-301 highlight the potential of ADCs as part of next-generation immunotherapy strategies. Despite promising results, several challenges remain. Resistance to immunotherapy, both primary and acquired, limits the durability of response in many patients. Research into mechanisms of resistance—including alterations in antigen presentation, immunosuppressive tumor microenvironments, and adaptive immune signaling—is crucial to extend the benefits of treatment. Furthermore, immune-related adverse events (irAEs), though manageable, pose significant risks that require specialized monitoring and interdisciplinary collaboration between oncologists, immunologists, and other healthcare providers. Global disparities also shape the discussion. While immunotherapy is increasingly accessible in high-income countries, cost, infrastructure, and biomarker testing

capacity remain barriers in low- and middle-income settings. These disparities raise ethical and policy concerns, as the greatest burden of cervical cancer occurs in resource-limited regions. Addressing affordability, expanding diagnostic capabilities, and supporting global partnerships are essential steps to ensure equity in access to life-saving therapies.

Table 1. Recent advances in immunotherapy for uterine and cervical cancers

Cancer type	Immunotherapy strategy	Key outcome
Uterine (endometrial)	Pembrolizumab + chemotherapy	Approved by NICE for advanced/recurrent cases; improved progression metrics
Cervical	Pembrolizumab + concurrent chemoradiotherapy (CCRT)	Significant reductions in death risk and disease progression (Keynote-A18)
Cervical	Tisotumab vedotin (antibody-drug conjugate)	Durable responses in recurrent/metastatic disease; FDA approval in refractory setting

The table summarizes three of the most significant and recent advances in the use of immunotherapy for uterine and cervical cancers. For uterine (endometrial) cancer, the combination of pembrolizumab with chemotherapy has recently gained strong clinical support and regulatory approval due to improved survival outcomes in advanced and recurrent cases. In cervical cancer, the Keynote-A18 trial confirmed that pembrolizumab combined with standard chemoradiotherapy significantly reduces the risk of disease progression and mortality, marking a milestone in first-line treatment. Additionally, tisotumab vedotin, an antibody-drug conjugate, has shown durable efficacy in heavily pretreated patients with recurrent or metastatic cervical cancer and has already received FDA approval.[9]

CONCLUSION

Despite these advances, challenges remain. Immunotherapy is not universally effective; resistance mechanisms, immune-related toxicities, and the need for reliable predictive biomarkers highlight the complexity of its application. Moreover, disparities in global access and the high cost of immunotherapy limit its availability in resource-constrained settings, where cervical cancer burden is greatest. Addressing these challenges requires not only scientific innovation but also health policy reform and international collaboration.

Overall, immunotherapy represents a transformative step toward personalized medicine in gynecologic oncology. As ongoing clinical trials continue to refine its use and as biomarkers become more sophisticated, the future holds promise for broader, safer, and more effective application of immunotherapy. With continued research, equitable access, and multidisciplinary approaches, immunotherapy has the potential to redefine standards of care and significantly improve the lives of women affected by uterine and cervical cancers worldwide.

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