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Advances in the Management of Cervical Cancer: Surgery, Systemic Therapy, and Immunotherapy

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Abstract:

Cervical cancer is a leading global health burden, especially in the context of low- and middle-income countries where screening and vaccination coverage are still low. Although prevention strategies have improved; however, the case for effective treatment modalities remain. Cervical cancer has undergone significant changes in its management since the introduction of multiple therapeutic options over the years. Management of early-stage disease can entail surgical options including conization, hysterectomy, trachelectomy, and pelvic exenteration. Radiotherapy with external beam radiation or brachytherapy remains fundamental to treatment and is frequently administered alongside chemotherapy aimed at improving sensitivity. For locally advanced and metastatic disease, chemotherapy (especially platinum-based regimens) is still the mainstay of treatment, and newer targeted therapies appear effective. In the last few years, immunotherapy has appeared as a revolutionary strategy, among the immune checkpoint inhibitors, therapeutic vaccines, and adoptive cell therapies showed promising results. Moreover, novel targeted therapeutics and combination approaches are being investigated in clinical trials, ushering in an era of personalized medicine for the cervical cancer patient population. Although these advancements lead to improved outcomes for patients, issues related to treatment selection, quality of life, fertility preservation, and access to care continue to be of utmost importance. This review summarizes the status of lock-in treatments in cervical cancer, illustrating both current use and future directions for established and emerging lock-in therapies, with an eye on their real-world clinical implementation and future directions.

Keywords:

Cervical cancer, Surgery, Radiation therapy, Chemotherapy, Immunotherapy, Targeted therapy, Personalized medicine, Clinical trials, Treatment strategies, Quality of life

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1. INTRODUCTION

Cervical cancer is the second most common gynecologic malignancy globally and the top cause of oncology-related morbidity and mortality in developing countries and in developing regions. Persistent infection with high-risk human papillomavirus (HPV) is the main risk factor, with HPV-16 and HPV-18 responsible for almost 70% of all cases. Despite the great achievements of preventative measures, such as the HPV vaccine and regular cervical screening programs, large numbers of women are still diagnosed at later stage disease when treatment is more complicated and prognosis is poorer [1].

Multimodal treatment approaches have become the standard of care for cervical cancer and the discussion of treatment options are therefore important. Surgery is the primary intervention for early stage disease, while radiotherapy and chemotherapy is the widely used intervention for locally advanced disease. Targeted therapies and immunotherapy are a couple of newer strategies over the past few decades that have led to improved survival and less toxicity in comparison with traditional therapies [2-3] . Nonetheless, choosing the ideal treatment for a patient requires personalized medicine approaches that account for parameters including but not limited to the tumor stage, histology, biomarker expression and the particular characteristics of the patient.

This Review will serve as a guide to the landscape of current treatments for cervical cancer, both established and experimental. We will review surgical approaches, radiation, chemotherapy, immunotherapy and new targeted agents, factors affecting treatment choices, quality of life issues and the direction of future research. Evidence from clinical trials and real-world data will be discussed to identify innovative treatment strategies that can be translated into clinical practice [4-5.]

Table 1: Summary of Current Treatment Modalities for Cervical Cancer

Treatment Modality	Indications	Advantages	Limitations	
Surgery (e.g., hysterectomy, trachelectomy)	Early-stage cervical cancer (IA–IB1)	Curative for localized tumors; fertility-preserving options available	Limited to early-stage disease; not suitable for advanced cases [6-7]	
Radiation Therapy (EBRT, Brachytherapy)	Locally advanced cervical cancer (IB2–IVA)	Effective in combination with chemotherapy; improves local tumor control	Risk of radiation-induced toxicity [8-9]	
Chemotherapy (Cisplatin, Carboplatin, Paclitaxel)	Advanced, recurrent, or metastatic cervical cancer	Can be used alone or with radiation; platinum-based regimens are effective	Systemic toxicity, resistance may develop [10-11]	

Immunotherapy (Pembrolizumab, Nivolumab)	Recurrent/metastatic PD-L1-positive cervical cancer	Durable response in selected patients; emerging role in combination therapy	Not effective for all patients; immune-related [12-13] adverse effects	
Targeted Therapy (Bevacizumab, PARP inhibitors)	Advanced cervical cancer with specific molecular markers	Personalized approach; improved outcomes in biomarker-positive patients	High cost; limited to selected patient populations [14-15]	

Cervical cancer is the second most common malignancy among women worldwide, with a higher burden in low- and middle-income countries (LMICs), translating to lower screening program coverage as well as access to human papilloma virus (HPV) vaccination. Although a worldwide effort to introduce and increase HPV vaccination has reduced cervical cancer incidence, late-stage diagnoses and poor survival continue to deserve attention in many settings because of inequitable access to quality health care [16].

Cervical cancer treatment has traditionally been defined by surgical and radiation therapy-based approaches, with radical hysterectomy and chemoradiation serving as standard therapies for localized and locally advanced disease. The role of systemic therapies has expanded, especially in patients with metastatic or recurrent disease. Although chemotherapy is still one of the main treatmentsthere has been a great change in the treatment landscape with the discovery of immunotherapy and targeted therapy [17].

Immune checkpoint inhibitors (ICIs), including pembrolizumab and nivolumab, have emerged as new treatment options for recurrent-metastatic cervical cancer, particularly in the subset of PD-L1-positive tumors. Understanding the diverse spectrum of immune-mediated adverse events has shown to be pivotal in informing management of patients treated with checkpoint blockade, which has been associated with durable responses, and has become a key component in the treatment of advanced cervical cancer [18]. Moreover, angiogenesis inhibitors, including quitizumab, have demonstrated improved survival outcomes in combination with platinum-based chemotherapy, which represents a significant advance in cervical cancer [19].

Personalized medicine is also gaining momentum, with biomarker-driven approaches serving an expanding role in informing treatment decisions. Next-generation sequencing (NGS) technologies have revealed important genomic markers like microsatellite instability (MSI), homologous recombination repair deficiency (HRD), and tumor mutation burden (TMB) which can guide treatment choice. Further research is being done to explore the potential applications of PARP inhibitors, tyrosine kinase inhibitors (TKIs), and new vaccine-based therapies to increase precision of treatment [19]. Furthermore, the implementation of liquid biopsy and next-generation sequencing (NGS) utilized to achieve real-time monitoring of treatment response and early recurrence detection is under investigation [20].

However, many hurdles still exist, including availability of new treatments. In resource-poor settings, where cervical cancer incidence is highest, high-cost immunotherapy and targeted

therapy are still beyond the reach of most patients. To decrease the mortality rate from cervical cancer, it will be critical to expand global efforts for screening, early detection, and cost-effective treatment options [21] . Future directions involve combinations of immunotherapy, radiation, and targeted agents, as well as artificial intelligence-enabled diagnostics and precision oncology approaches to improve treatment potency and promote long-term patient survival [22].

However, the treatment paradigm for cervical cancer is evolving to be more patient-oriented and biomarker-driven, given the need to improve survival outcomes with less treatment-associated toxicity as research continues to identify new therapeutic targets [23]. The future of cervical cancer treatment looks promising, with data from ongoing clinical trials of novel drug combinations and immunotherapeutic strategies [24].

SURGICAL TREATMENTS

Surgery is an essential part of early-stage cervical cancer management and provides curative option for patients with localized disease. The surgical approach is determined based on tumor size, stage, histological type, and lymph node involvement, and also taking into account fertility preservation strategies. Surgery can be as simple as a minimally invasive approach with few changes in diet to an extensive procedure to remove locally advanced tumors. Here are the important options for cervical cancer surgery [25].

Conization

Cold knife conization: Also known as conization or loop electrosurgical excision procedure (LEEP), this technique preserves fertility and is indicated for female patients with early-stage cervical cancer or precancerous lesions (cervical intraepithelial neoplasia - CIN). It entails the excision of a cone-shaped portion of the cervix housing diseased cells while sparing the remaining uterus. It is the procedure of choice for stage IA1 squamous or adenocarcinoma in one of our notes (figure 1, table 2) where it is stated that lymph vascular space invasion must be absent. Conization despite being a viable and ideal choice for young women as it reconfirms high cure rates with also retaining reproductive potential. However, this poses risks of cervical stenosis, elevated rates of miscarriage, as well as preterm labor in subsequent pregnancies. [26]

Hysterectomy (simple and radical)

Hysterectomy (surgical removal of the uterus) is a definitive treatment for early-stage cervical cancer (stages IA2-IB1). The procedure can be explained into:

Simple Hysterectomy: (removal of the uterus and cervix without removal of parametrial tissues and vagina) It is usually completed for stage IA1 cancer without lymphovascular invasion or for persistent high-grade CIN (cervical intraepithelial neoplasia) not suitable for conization (which is measure widely taken to remove cervical cancer) [27].

Types of radical hysterectomy (Type III or Wertheim's procedure) — the procedure removes the uterus, the cervix, the upper part of the vagina, the surrounding parametrial tissues, and pelvic lymphadenectomy. It is approved for stage IA2 to IB1 cervical cancer and gives excellent local tumor control. However, minimally invasive techniques such as robot-assisted and laparoscopic radical hysterectomy have been increasingly adopted owing to improved recovery times and

less surgical morbidity, even though recent data indicate that open surgery might achieve better oncological outcomes [28].

Trachelectomy

For women wishing to conceive in the future, radical trachelectomy is a fertility-sparing alternative. This retains the uterus and the ovaries, hence enabling the woman for subsequent conception . This is mainly applied for stage IA2 to IB1 tumors ≤2 cm. There are two main types of trachelectomy:

- Radical vaginal trachelectomy (RVT): Carried out via the vaginal route, most commonly associated with laparoscopic lymphadenectomy.
- Radical abdominal trachelectomy (RAT): This approach is performed through the abdominal route allowing exposure to respect the tumor but with a slightly increased rate of complications.

Pregnancy rates after trachelectomy are about 50% and are often complicated by premature labor and cervical incompetence. However, oncologic outcomes are comparable to those obtained with radical hysterectomy in well-selected patients [29].

Pelvic Exenteration

Pelvic exenteration is a salvage procedure used in the context of recurrent or persistent cervical cancer following radiation therapy. It is a radical operation that entails removing all pelvic organs: attaching the anterior exenteration (removal of the uterus, cervix, and vagina, and bladder), the posterior exenteration (removal of the rectum), or both (total exenteration). Such an approach is reserved for highly selected patients with localized recurrences in the absence of distant metastases [30].

So, despite the fact that pelvic exenteration can carry a high burden of morbidity, with continued advancements in surgical techniques have contributed to improved five-year survival suitable patients of around 40- 60%. Reconstructive methods, namely myocutaneous flap neovaginal reconstruction, have also led to improved quality of life [31].

Cervical cancer is a potentially curable disease with operable disease and surgical treatment. The choice of such a procedure is determined by the stage of the tumor, question of preservation of fertility, and whether or not there is recurrent disease. Although minimally invasive approaches are continuously born, open surgery is still a gold standard in radical approaches for cervical malignancies. [32]

RADIATION THERAPY

Chemotherapy and radiation therapy play a major role in cervical cancer treatment, especially in patients with locally advanced disease or those ineligible for surgical intervention. It is frequently used in conjunction with chemotherapy (chemoradiation) to optimize treatment effectiveness. Radiation therapy acts by injuring the DNA of neoplastic cells, which leads to their death with little damage to adjacent healthy tissues. The treatment of cervical cancer includes external beam radiation therapy (EBRT) and brachytherapy, either alone or in combination. [33]

External Beam Radiation Therapy (EBRT)

EBRT itself is a non-invasive local regional treatment that uses high-energy X-rays directed at the pelvis to treat the primary tumor and any potential sites of microscopic disease expansion. It is widely used in treatment of locally advanced cervical cancer (stages IB2 to IVA) and administered in a series of fractions for 5 to 6 wk . For patients with high-risk features (non-organ confined disease), neoadjuvant chemotherapy has improved precision and leads to overcome in long-term (e.g., bladder, rectum, and bowel). IMRT has been shown in studies to sharply reduce the likelihood of both gastrointestinal and genitourinary toxicities, thus bettering the patient's quality of life [34].

Brachytherapy

Cervical cancer is treated with a combination of external beam radiation therapy and brachytherapy, high-dose radiation in direct contact with the tumor site through the use of intracavitary or interstitial applicators. High efficacy of immunity against this deadly disease has been concluded for EBRT in local control and better survival. High-dose rate (HDR) brachytherapy is preferred for treatment duration and minimized radiation exposure to healthcare personnel compared to low-dose rate (LDR) brachytherapy, giving sessions of short, dated irradiation. Studies have shown that adding brachytherapy to treatment regimens significantly improves local tumor control and overall survival, with 5-year rates over 60% in stage IIB-IVA patients [35].

Chemoradiation (Combination Chemotherapy and Radiotherapy)

The standard of care for locally advanced cervical cancer is concurrent chemoradiation, which incorporates radiation therapy with chemotherapy. The drug of choice is cisplatin-based chemotherapy, which acts as a radiosensitizer, potentiating the effect of radiation [36]. Several clinical trials, including the landmark Gynecologic Oncology Group (GOG) trials, have shown a significant benefit in overall survival and progression-free survival with concurrent chemoradiation compared to radiation therapy alone . While chemoradiation is beneficial, it is associated with increased rates of toxicity such as hematologic suppression, gastrointestinal distress, and nephrotoxicity, making careful patient selection and supportive care measures essential [37].

Radiation therapy, especially when combined with chemotherapy, continues to play a crucial role in the treatment of cervical cancer. Technological advances in the delivery of radiation including IMRT and brachytherapy have increased treatment accuracy and reduced toxicity. Further research is required to improve radiation protocols, maximize outcomes, and reduce long-term side effects [38].

CHEMOTHERAPY

Cervical cancer, especially locally advanced, recurrent, and metastatic diseases is one of the diseases in which chemotherapy is the main component of treatment. It is given with radiation therapy (chemoradiation) for locally advanced disease, as neoadjuvant therapy prior to surgery, or for palliative care for metastatic disease. Chemotherapy is effective according to tumor stage, histology, and patient-specific factors, therefore treatment selection should be individualized [39].

Standard Chemotherapy Agents

The most common treatment regimens for cervical cancer are platinum-based chemotherapies (mostly cisplatin). Cisplatin- and 5-FU-based concurrent chemoradiation has been proven to enhance radiosensitivity and remains the standard of care for locally advanced cervical cancer, supporting improved response and survival rates. Studies demonstrated a remarkable improvement in both progression free survival (PFS) and overall survival (OS) when using weekly cisplatin at 40 mg/m² along with radiation as compared to the use of radiation alone. Carboplatin is an alternative with a better toxicity profile for patients who cannot tolerate cisplatin. [40]

Combination chemotherapy regimens, for example cisplatin plus paclitaxel or topotecan plus paclitaxel, have been associated with better response rates in patients with recurrent or metastatic cervical cancer [41]. Bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF), has been shown to improve survival when added to platinum-based chemotherapy, with studies reporting an increase in median overall survival of 3.7 months over chemotherapy alone [42].

Targeted Therapies

However, targeted therapy has now become a new and important strategy for advanced and recurrent cervical cancer, including targeting specific molecular pathways activated during progression of the tumor. Inhibition of tumor angiogenesis by the anti-VEGF monoclonal antibody bevacizumab was the first targeted agent approved in the setting of cervical cancer, improving survival when used in combination with cisplatin and paclitaxel [43].

Recent advances such as anti-angiogenic therapy and immune checkpoint inhibitors, like pembrolizumab (anti-PD-1), have shown long-lasting responses in patients with PD-L1 positive cervical cancer. The positive phase II cohort of KEYNOTE-158 observed a superior ORR and OS for patients with recurrent or metastatic disease [44] .Thus, PD-L1-positive cervical cancer has been FDA-approved for pembrolizumab.

Investigational targeted therapies include TKIs and the class of drugs known as PARP inhibitors, which are currently being evaluated in clinical trials for their role in combination with chemotherapy and immunotherapy [45] .

Chemotherapy is still an important treatment option for cervical cancer, particularly in patients with locally advanced and metastatic disease. Although platinum-based regimens still represent the mainstay, the field has seen an increasingly prominent role for targeted therapies, such as those targeting leukocyte infiltration anti-VEGF and immune checkpoint inhibition, in improving survival. Figure 1 , With treatment combinations, minimizing toxicity remains a goal of future studies, which are setting the stage for more effective, new therapy and strategies [46] .

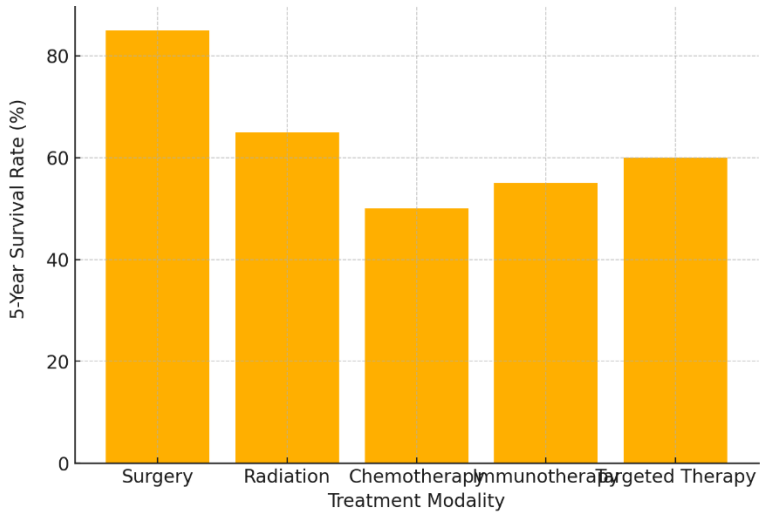

Figure 2: Survival Outcomes in Cervical Cancer Based on Treatment Approach

IMMUNOTHERAPY

Immunotherapy represents a major breakthrough in the management of cervical cancer, especially for recurrent and metastatic disease that has failed conventional therapies. Since persistent human papillomavirus (HPV) infection is a key etiological factor driving the development of cervical cancer, an obvious immunotherapeutic strategy has thus focused on boosting anti-cancer immune responses toward HPV-infected tumor cells [47] . Common immunotherapy modalities include checkpoint inhibitors, therapeutic vaccines, and adoptive cell therapies, that have demonstrated encouraging results in clinical trials [48] .

Checkpoint Inhibitors

Checkpoint inhibitors are one of the most successful immunotherapy strategies in cervical cancer. Tumor cells can evade the immune system using immune checkpoint pathways, such as programmed death-1 (PD-1) and programmed death-ligand 1 (PD-L1) that inhibit T-cell activation and tumor growth [49] .

Pembrolizumab, a) an anti-PD-1-monoclonal antibody, has been beneficial to patients with PD-L1-positive recurrent or metastatic cervical cancer. Study KEYNOTE-158 showed that pembrolizumab significantly extended progression-free survival (PFS) and overall survival (OS), resulting in FDA approval for PD-L1 positive cervical cancer. Another PD-1 inhibitor, nivolumab, is under investigation in combination with chemotherapy and radiation therapy for locally advanced disease [50] .

Checkpoint inhibitors have also been studied in combination regimens with other therapeutics to augment treatment responses. Studies for atezolizumab (anti-PD-L1) in combination with bevacizumab and chemotherapy, for example, have shown higher immune activation and prolonged survival [51] .

Therapeutic Vaccines

In contrast to prophylactic HPV vaccines (which prevent HPV infection), therapeutic vaccines aim to activate the immune system to target existing HPV-infected tumor cells. The purpose of

these vaccines is to induce a T-cell immune response against HPV oncoproteins, specifically E6 and E7, which helps the tumor survive and proliferate [52].

VGX-3100, a DNA-based therapeutic vaccine, is one such promising candidate, demonstrating positive results in generating immune responses against cervical precancerous lesions associated with HPV. Phase I/II studies have indicated that therapeutic vaccination may be an alternative for early-stage cervical cancer and an adjunct to other therapies in advanced disease . Meanwhile, additional investigational vaccines, including ISA101 and GX-188E, have been studied in combination with checkpoint inhibitors to augment immune responses [53].

Adoptive Cell Therapies

Adoptive cell therapy (ACT) is the next generation of immunotherapy where a patient's immune cells are customized to be able to identify and kill tumor cells. Among them, one of the most promising ACT approaches applied in cervical cancer is tumor-infiltrating lymphocyte (TIL) therapy, in which T cells are harvested from the tumor, cultured with high-dose IL-2, and re-infused to the patient to augment the anti-tumor response [54].

TIL therapy has been shown to cause complete and durable responses in patients with metastatic cervical cancer, especially after chemotherapy and radiation therapy failure. Several ongoing trials also investigate the role of CAR-T cell therapy in which patients own T lymphocytes are genetically modified to specifically target HPV related tumor antigens, emerging as a promising strategy for future treatment [55].

The isolation of specific antigens has led to great strides forward in cancer treatment, including cervical cancer, where immunotherapy has dramatically improved outcomes in subgroups of patients with recurrent and advanced disease. Checkpoint inhibitors, therapeutic vaccines and adoptive cell therapies are proving clinically efficient, and research continues into combining these newer modalities with current approaches to improve total therapeutic outcome. Immunotherapy will also play an important role in the era of personalized medicine, with hopes of improving response and survival rates among cervical cancer patients [56].

2. CURRENT MEDICINE USED IN TREATMENT OF CERVICAL CANCER

Cervical cancer management has undergone a major transformation with conventional chemotherapy, targeted therapy and immunotherapy providing significant impact on survival and quality of life. Selection of medication is based on tumor stage, histology, patient status, and biomarker status. The major drug classes currently being utilized in cervical cancer are as detailed below.

Platinum-Based Chemotherapy

Cispatin is the most frequently used chemotherapeutic drug in cervical cancer and is an important ingredient in Concurrent Chemoradiation therapy (CCRT) for locally advanced disease. As a radiosensitizer, it is capable of inducing DNA damage in tumor cells to increase the efficacy of radiation therapy . There is also extensive usage of cisplatin in metastatic and recurrent cervical cancer; cisplatin in monotherapy or combination with paclitaxel [57].

Cisplatin is contraindicated in the setting of nephrotoxicity/neurotoxicity, and carboplatin is an alternative used in those patients. In that respect, it has demonstrated similar efficacy with a more favorable toxicity profile, rendering it a preferential choice for various patients [58].

Taxane-Based Chemotherapy

Paclitaxel, a microtubule inhibitor, is commonly used in combination with cisplatin or carboplatin for patients with recurrent or metastatic cervical cancer [59]. It inhibits mitosis and induces apoptosis in tumor cells. Docetaxel, another taxane, is occasionally used as a substitute, though it is not used as commonly in cervical cancer [60].

Topoisomerase Inhibitors

Topoisomerase I inhibitor topotecan shows synergistic effect when combined with cisplatin and has improved progress-free survival (PFS) in metastatic cervical cancer. This is especially the case for second-line settings, when tumors become resistant to treatment with platinum-based therapies [61].

Anti-Angiogenic Therapy

Introduction: Bevacizumab, an anti-vascular endothelial growth factor (VEGF) monoclonal antibody has been shown to improve survival in women diagnosed with advanced and monastic cervical cancer. This has prolonged overall survival (OS) by inhibiting tumor angiogenesis when used with cisplatin and paclitaxel. It was the first targeted therapy approved for persistent, recurrent, or metastatic cervical cancer and is still an important option in clinical practice. [62]

Immune Checkpoint Inhibitors

Checkpoint inhibitors have transformed the treatment of cervical cancer, particularly for PD-L1-positive tumors.

- Pembrolizumab (anti-PD-1 monoclonal antibody) was approved for PD-L1-positive recurrent or metastatic cervical cancer based on the KEYNOTE-158 trial, which demonstrated durable responses and improved survival.
- Locally advanced nivolumab (anti-PD-1 inhibitor) and Atezolizumab (anti-PD-L1 inhibitor) are being studied in combination with chemotherapy and radiation therapy.

Investigational and Emerging Therapies

Clinical trials are continuously evaluating new treatment options, including:

- PARP inhibitors (e.g; Olaparib), which target defective DNA repair mechanisms
- Tyrosine kinase inhibitors (TKIs) are under evaluation alone or in combination with chemotherapy and immunotherapy.
- Therapeutic vaccines (e.g., VGX-3100) that can destroy HPV-infected cells prior to the development of cancer.

This is a well-marked out space for cervical cancer pharmacology including platinum-based chemotherapeutics, taxanes, topoisomerase inhibitors, a plethora of targeted therapies and immunotherapy. With the advent of bevacizumab and pembrolizumab, treatment of patients with advanced and metastatic disease has been revolutionized, and ongoing clinical trials are continuing to refine treatment algorithms. As research progresses, it is anticipated that these

agents, when combined with newer targeted agents and others in the realm of immunotherapy, will improve survival and other treatment outcomes [63] .

3. EMERGING TREATMENTS AND CLINICAL TRIALS

Novel Tenticaps, pyrotinib and transfusion therapy are some of the newer targeted therapies along with combination approaches that are showing promise in cervical cancer treatment, heralding an exciting time to improve cancer outcomes. Platinum-based chemotherapy and radiation therapy remain the mainstay of treatment; however, the advent of targeted therapies, immunotherapy and molecular based treatment strategies are changing this paradigm. These novel therapies are being investigated in clinical trials to improve survival rates, reduce toxicities, and provide more tailored treatment options for women with cervical cancer.

Novel Targeted Therapies

Molecular profiling of cervical cancer over the last decade has revealed important genetic pathways amenable to therapeutic targeting. The most promising types of targeted therapies include angiogenesis inhibitors, poly (ADP-ribose) polymerase (PARP) inhibitors, and tyrosine kinase inhibitors (TKIs).

- Bevacizumab (VEGF antagonist): Bevacizumab (anti-VEGF) is currently approved for recurrent and metastatic cervical cancer and is also being studied in combination with immune checkpoint inhibitors and chemotherapy.
- Poly (ADP-ribose) polymerase (PARP) inhibitors: PARP inhibitors like Olaparib and niraparib are being studied for patients with defective DNA repair systems. Through the blocking of damage repair pathways critical for tumor cell survival, these drugs capitalize on tumor cell vulnerabilities and induce cancer cell death.
- Tyrosine kinase inhibitors (TKIs): pazopanib and Lenvatinib are investigated for advanced cervical cancer especially in PI3K/AKT/mTOR pathway alterations positivity.

Investigational targeted therapies also include agents that block epidermal growth factor receptors (EGFR) and fibroblast growth factor receptors (FGFR), both of which are overexpressed in some cervical cancers, and whose activity leads to tumor cell growth. [64] Figure 3

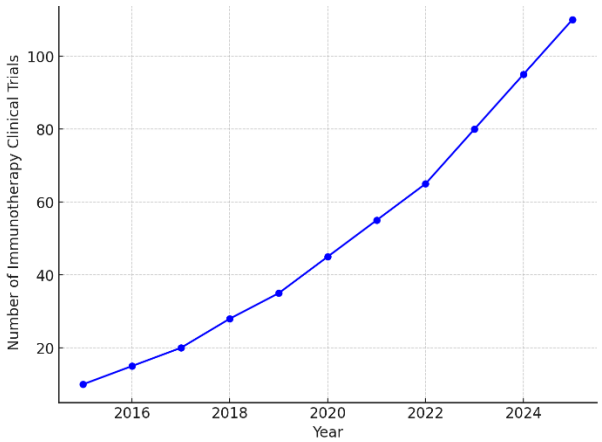

Figure 4: Trends in Immunotherapy Clinical Trials for Cervical Cancer (2015-2025)

Combination Approaches

Since then, combination therapy has become a major focus of clinical investigation, intending to optimize therapeutic effect by the combination of chemotherapy, immunotherapy, radiation and targeted therapies. The following ongoing trials are assessing these combinations:

- Checkpoint Inhibitors + Chemotherapy: In PD-L1-positive cervical cancer, pembrolizumab (PD-1 inhibitor)/platinum-based chemotherapy combination offers improved overall response rates and progression-free survival. This combination is being evaluated by the KEYNOTE-A18 trial in locally advanced cervical cancer patients treated with chemoradiation.
- Immunotherapy+ Angiogenesis Inhibitors: Such as postulated on BEATcc, bevacizumab + atezolizumab (PD-L1 inhibitor) with chemotherapy, to induce higher immune system activation and to prevent tumor angiogenesis.
- Radiotherapy + Immunotherapy — The combination of radiation therapy with immune checkpoint inhibitors is another promising approach. DISCLAIMER: The views expressed in this article are those of the authors and do not necessarily represent those of any organization. Because radiation kills tumor cells and releases tumor antigens, it may enhance the immune response when combined with nivolumab or pembrolizumab.
- Targeted Therapy + Chemotherapy: Several trials are investigating the role of PARP inhibitors with cisplatin-based chemotherapy in individuals with homologous recombination deficiency (HRD), a genetic signature that occurs in a subset of cervical cancer [65].

4. TREATMENT SELECTION AND PERSONALIZED MEDICINE

Choice of effective intervention for cervical cancer is determined by various factors such as tumor stage, histotype, health status of the patient, and biomarker expression. However, advances in genetic profiling and biomarker-driven therapies are revolutionizing the management of cervical cancer by enabling individualized therapies that amplify efficacy while reducing toxicity. Hence, personalized medicine seeks to optimize treatment regimens according to the molecular features of the tumor, which are associated with better survival outcomes and less toxicity [66].

Tumor stage and disease extent are the primary determinants for treatment decisions. Surgical treatment options for clinical early-stage cervical cancer (≤stage IIA) include conization, trachelectomy, and hysterectomy, and chemoradiation remains the standard of care for locally advanced cervical cancer (stages IIB and IVA). Patients with metastatic or recurrent disease may require systemic chemotherapy, targeted therapy, or immunotherapy depending on their biomarker status. The histological distinctions also determine the treatment response, as squamous cell carcinoma (SCC) is more radio-sensitive compared to adenocarcinoma and may need alternative approaches for therapy [67].

Factors including age, fertility goals, performance status, and comorbidities are essential for guiding treatment decisions. In younger patients diagnosed with early-stage disease, radical trachelectomy may be considered in place of hysterectomy if fertility preservation is desired,

while older patients or patients with significant comorbid conditions may be better candidates for radiotherapy-based strategies. Moreover, some therapy comes with a specific risk associated with it; for instance, cisplatin-based chemoradiation is contraindicated in patients with renal dysfunction, so other regimens like carboplatin-based chemotherapy should be used.

Biomarkers and genetic profiling are playing an increasing role in how treatment decisions are made in cervical cancer. PD-L1 expression, for example, became a master biomarker for determining immunotherapy eligibility. The PD-L1 positive tumors exhibit enhanced response to the checkpoint inhibitors such as pembrolizumab, as seen in the KEYNOTE-158 trial, which led to its approval in the setting of recurrent and metastatic cervical cancer. Tumors with high tumor mutation burden (TMB) or microsatellite instability (MSI) also have increased likelihood of response to immune checkpoint inhibitors, presenting an additional opportunity for personalized treatment [68].

Genomic analysis has also revealed genetic alterations associated with aberrant angiogenesis representing potential therapeutic targets and polyclonal targeting of aberrant VEGF signaling for anti-angiogenic therapy. Toxicities associated with bevacizumab, a VEGF inhibitor shown to provide a significant increase in survival when given in combination with platinum-based chemotherapy in metastatic cervical cancer, have led to its inclusion in treatment guidelines. Further, other molecular targets, including homologous recombination deficiency (HRD) and BRCA mutations, have enabled the investigation of PARP inhibitors (e.g., Olaparib, niraparib), which have also been investigated in clinical trials for HRD-positive cervical cancer.

Advances in cervical cancer treatment have focused on personalized medicine, with many ongoing clinical trials including studies of combinations of targeted therapy, immunotherapy, and chemotherapy. Additional refinement of treatment selection will occur over the next few years with the use of liquid biopsy and next-generation sequencing (NGS) (29) to identify circulating tumor DNA (ctDNA) and emerging biomarkers. As these approaches mature, individualized treatment protocols will facilitate enhanced control of disease, an increase in survival, and less toxicities associated with treatment, and thereby improved outcomes overall among patients [69].

5. QUALITY OF LIFE CONSIDERATIONS

Management of cervical cytology has important implications for patient quality of life, both physiologically and psychologically. Even with progress in surgery, radiation, chemotherapy, and more recently, immunotherapy, cure or long-term survival remains the exception rather than the rule, and these treatments frequently leave behind long-term sequelae and complications that get in the way of daily function and quality of life. Management of treatment-related toxicities, fertility preservation, and psychosocial implications are an integral part of providing thorough care for women with cervical cancer [70].

Side effects from treatment differ according to the treatment received and its intensity. Surgical procedures such as hysterectomy or pelvic exenteration can result in pelvic pain, urinary dysfunction, sexual dysfunction, and bowel disturbances, dramatically changing a patient's lifestyle. Chronic gastrointestinal and genitourinary toxicity, including diarrhea, bladder

irritation, and radiation-induced fibrosis, has commonly been noted with radiation therapy, especially in the pelvic regions. Chemotherapy toxicity can be debilitating, comprising fatigue, nausea and vomiting, peripheral neuropathy and immunosuppression, which can further impair quality of life. It is important to monitor and manage immune-related adverse events during immunotherapy treatment, including thyroid dysfunction, colitis, and pneumonitis .

Fertility preservation is one of the most urgent issues facing younger cervical cancer patients. Infertility is irreversible following radical solutions (hysterectomy and pelvic radiation); thus, fertility-sparing strategies are an integral part of treatment planning. A fertility-sparing option for early-stage disease, trachelectomy, which is the excision of the cervix but preserving the uterus, has been offered. Some patients may consider oocyte or embryo cryopreservation before beginning chemotherapy or radiation treatment to preserve reproductive options in the future. Nonetheless, even with fertility preservation methods, survivors face challenges such as preterm labor and cervical insufficiency related to pregnancy [71] .

However, psychosocial and emotional issues are also key elements of the post-treatment phase, beyond physical complications. Cervical cancer survivors suffer from depression, anxiety and body image issues as a result of surgical scarring, sexual dysfunction and the emotional toll of their cancer diagnosis. Sexual dysfunction (e.g., vaginal dryness, loss of libido, dyspareunia) is especially prevalent among women who have received radiation therapy or underwent radical surgery. Counseling, pelvic floor therapy, hormone replacement therapy, and psychosexual interventions are all interventions that have been shown to mitigate these issues and improve quality of life after treatment [72] .

Quality of life, which is critical to addressing, needs an interdisciplinary approach involving oncologists, psychonco-logists, fertility specialists, palliative care specialists, etc. Programs that provide supportive care with an emphasis on pain management, mental health counselling, rehabilitation and lifestyle interventions can allow patients to deal with the difficulties of treatment and survivorship. Future studies exploring low toxicity treatment regimens, psychobiology interventions, and complementary integrative medicine approaches to health and well-being will only serve to enhance the life experience of women dealing with cervical cancer [73] . Table 2

Table 3: Common Side Effects of Cervical Cancer Treatments and Their Management

Treatment Modality	Common Side Effects	Management Strategies	
Surgery	Pain, urinary dysfunction, sexual dysfunction	Pain management, pelvic floor exercises, hormone replacement therapy [74-75]	
Radiation Therapy	Gastrointestinal toxicity, vaginal stenosis, bladder irritation	Dietary modifications, hydration, vaginal dilators [76-77]	
Chemotherapy	Nausea, fatigue, myelosuppression	Anti-emetics, dose adjustments, supportive care [78]	
Immunotherapy	Immune-related adverse events	Corticosteroids, immune-	

	(colitis, thyroid dysfunction)	modulating agents [79]	
Targeted Therapy	Hypertension, bleeding risks (Bevacizumab), anemia (PARP inhibitors)	Blood pressure monitoring, iron supplementation [80]	

6. FUTURE DIRECTIONS AND CHALLENGES

New approaches for treating cervical cancer swiftly evolve including targeted therapies, immunotherapy and precision medicine. Although great strides have been achieved in optimization of survival, continued research primarily aims to adapt existing treatment regimens, identify new treatment targets, and improve early-detection strategies. Nevertheless, treatment access barriers, healthcare disparities, and financial constraints continue to be significant hurdles to achieving equitable care for all patients [81] .

One key focus of active research is novel immunotherapy and combination treatment strategies. Checkpoint inhibitors, including pembrolizumab and nivolumab, have already had some success in PD-L1-positive cervical cancer, but ongoing studies are looking at combination approaches with other agents, including anti-VEGF therapies (bevacizumab) and PARP inhibitors (olaparib, niraparib). These multi-target strategies are designed to circumvent mechanisms of resistance and augment durable response rates in advanced cervical cancer. Moreover, the development of personalized cancer vaccines is growing, including VGX-3100, and ISA101; these vaccines are aimed at inducing an immune response specific to a patient0s tumor [82] .

“We are also interested in looking at the use of predictive biomarkers for treatment selection. PD-L1 expression, VEGF overexpression, and TMB guides therapy selection — but recent discoveries like ctDNA and TILs may identify patients whom will benefit most from specific therapy. The implementation of next-generation sequencing (NGS) and liquid biopsies in clinical practice may additionally enable early diagnosis and monitoring of recurrences as well as on-demand treatment adjustments [83] .

Though these empowering changes have happened, still many challenges remain, especially in accessing treatment. Access to screening, diagnostic services, and treatment advancements remains limited in low- and middle-income countries (LMICs), where the burden of cervical cancer is highest. A major barrier to their use is cost, as most patients cannot pay for expensive drugs like checkpoint inhibitors or anti-angiogenic agents. Some significant steps towards reducing this divide in treatment disparities would include: Increasing universal healthcare coverage, negotiating drug pricing and enhancing funding for cervical cancer programmed [84] .

Inadequate infrastructure for advanced radiation therapy techniques like intensity-modulated radiation therapy (IMRT) and image-guided brachytherapy (IGBT) in resource-limited environments leads to ineffectual radiation therapy delivery to many patients. There is a need to expand radiation oncology centers, train healthcare professionals, and establish cost-effective models of treatment to enhance access to quality cancer care across the globe [85] .

Research on minimally invasive and fertility-sparing techniques is also expanding, especially for younger patients diagnosed with early-stage cervical cancer. Current strategies aimed at preserving reproductive potential without compromising oncologic outcomes include radical

trachelectomy, neoadjuvant chemotherapy with subsequent fertility sparing surgery, and uterine transplantation.

However, focused efforts on removing treatment access barriers, developing low-cost therapeutic approaches, and improving healthcare infrastructure will still play a key role in reducing global cervical cancer mortality. Advancements in risk-based screening as well as the adoption of artificial intelligence (AI) and digital health technologies are likely to transform early detection and risk stratification and, therefore, contribute to individualized treatment strategies [86].

7. CONCLUSION

Cervical cancer is still a global health challenge, especially in low- and middle-income countries, where screening and advanced treatment are often not accessible. Although substantial advancements have been made in surgery, radiation therapy, chemotherapy and immunotherapy, treatment options for cervical cancer remain an area of growth, with the new generation of targeted therapies and precision medicine strategies providing promising avenues for exploration. This review elucidated on the current treatment landscape with the use of standard interventions like radical hysterectomy, chemoradiation and systemic therapy along novel advancements in checkpoints inhibitors, targeted therapy, and personalized medicine.

Surgical approaches are the mainstay of therapy for early-stage cervical cancer, and conization, trachelectomy, and hysterectomy all have curative potential. The most effective method for locally advanced disease is radiation therapy (especially chemoradiation). Oncologic outcomes improved greatly, perhaps as a result of better delivery systems of the radiotherapy (e.g., intensity-modulated radiation therapy (IMRT), image-guided brachytherapy (IGBT)) and reduced toxicities. Platinum-based chemotherapy, taxanes, and angiogenesis inhibitors (e.g. bevacizumab) remain the cornerstones of systemic therapy for both metastatic and recurrent cervical cancer.

Over the past decade, immunotherapy with PD-1/PD-L1 blockade has proved increasingly transformative for the treatment of recurrent and metastatic cervical cancer. Pembrolizumab has shown a gross survival benefit in PD-L1-positive, and trials are ongoing with chemotherapy and radiation therapy. Also, agents targeting certain molecular subtypes of cervical cancer, including PARP inhibitors and tyrosine kinase inhibitors (TKIs), are being investigated for their potential in treating.

Notwithstanding the improvements made, commentaries highlighted few challenges in the realm of treatment availability and affordability of novel therapeutics, as well as healthcare infrastructure weak spots in low- and middle-income settings. Increasing HPV vaccination programs worldwide, enhancing screening programs, and promoting affordable cancer treatment access are crucial to decreasing the incidence and mortality of cervical cancer. Moreover, next-generation sequencing (NGS) combined with a thorough understanding of biomarker research would continue to streamlining personalized treatment approaches..

Abstract: The future of cervical cancer treatment is a multidisciplinary and patient-centric approach combining immunotherapy, targeted therapy, and AI-based diagnostic tools. The aim

is a more effective, less toxic, globally available treatment of all patients with cervical cancer, as scientific studies develop creative combination therapies and new drugs targets. Continuing to close treatment gaps, funding new therapeutic developments and investing in personalized treatment plans are anticipated to bring markedly improved outcomes in cervical cancer in the next few decades.

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