A COMPREHENSIVE EXPLORATION OF ADVANCES IN CERVICAL CANCER TREATMENT: TARGETED THERAPY, RADIOTHERAPY AND CHEMOTHERAPY

SRI, U. N. S.[1] – METTA, S.[1*] – AISHWARYA, M.[1] – PRIZLY, G.[1] – KUSUMA, C.[1] – LOKESH, N.[2]

[1] *Department of Pharmaceutics, Marri Laxman Reddy Institute of Pharmacy, Telangana, India.*

[2] *Sree Dattha Institute of Pharmacy, Telangana, India.*

**Corresponding author*
e-mail: samyumetta2204[at]gmail.com

(Received 06th May 2024; Revised 14th July 2024; accepted 23rd July 2024)

Abstract. Cancer is a complex group of diseases characterized by the uncontrolled growth and spread of abnormal cells. These cells can invade and destroy normal tissues and can also spread to other parts of the body through the bloodstream and lymphatic system. The development of cancer involves genetic mutations that disrupt the normal regulation of cell growth, leading to the formation of tumors. These tumors are of two types which describe the behaviour of tumor. They are benign and malignant. Malignant tumors can metastasize, or spread into, neighboring tissues, and can also generate new tumors by traveling to far-off regions of the body. Malignant tumors is another term for cancerous tumors, benign tumors do not penetrate or spread to neighboring tissues. Benign tumors typically don't recur after removal. There exist more than 100 distinct types of cancer, each designated by the specific cell type or organ of origin. Each variation is characterized by unique causal factors, and cancer, being a preventable and treatable ailment, exhibits improved outcomes through early detection via screening. This research paper provides a comprehensive overview of cervical cancer, encompassing its epidemiology, risk factors, and cutting-edge advancements in preventive and therapeutic strategies. Beyond conventional approaches, such as surgery and chemotherapy, the paper examines the efficacy and potential of targeted therapy, radiation therapy, and immunotherapy in combating cervical cancer. These therapeutic strategies offer hopeful paths for individualized treatment, leading to enhanced outcomes for patients.
Keywords: *cancer, benign, malignant, cervical cancer*

Introduction

Cervical cancer is a serious health condition. It develops in women's cervix. It is the second most common malignant disease and millions of women are diagnosed with cervical cancer. Mostly 500,000 women were diagnosed with the disease and nearly 300,000 where died each year worldwide. The discovery of new anticancer agents, interfering with molecular targets expressed by the tumor's micro-environment or by the tumor cell itself, represents a possible chance for the struggle against this tumor. And in the urgent demand for novel effective therapies both as the first and the second line treatment for these patients, immunotherapy is developing fast and has made some achievements. Concerning chemotherapy, up until recently, single-agent cisplatin stood as the preferred drug for metastatic cervical cancer. However, various combinations, such as doublets and triplets, have exhibited superior objective response rates compared to single-agent cisplatin. Virus, parasites, and bacteria are the major risk factors for progression and development of different types of cancer. Cervical cancer is caused by sexually transmitted human papillomavirus. Human papillomavirus (HPV), comprises a large family of viruses with numerous types (HPV 6, 11, 16, 18, 31, 33, 45, 53, 58), classified as either high-risk or low risk based on their association with certain cancers

which are transmitted through sexual contact. HPV types 16 and 18 (Vesco et al., 2011) are particularly implicated in cervical cancer development.

Early stages of cervical cancer may not cause noticeable symptoms. As the cancer progresses, symptoms may include: Pain in Lower abdomen, foul smelling discharge, inter-menstrual bleeding, weightless, abnormal vaginal discharge, urine urgency, bleeding per vagina, pelvic pain or pain during intercourse. To comprehend cervical cancer, we examine its occurrence in populations, identify contributing factors, and explore cellular changes through the lenses of epidemiology, etiology, and pathophysiology.

Discussion

Literature review

The human papillomavirus is the most common cause of cervical cancer. This virus is also responsible for cervix, vulva, vaginal, anus, and penis malignancies. A typical cell proliferation in the cervix is the cause of cervical cancer. The lower end of the uterus is called the cervix. The tissue that joins the uterus and vagina is called the cervix. Prior to the disease's progression, the cervix's cells undergo a condition known as dysplasia, in which abnormal cells begin to develop in the cervical tissue. These abnormal cells continue to proliferate, resulting in the formation of a tumour around the cervix (Crosbie et al., 2013). Yang et al. (2019) investigated the effect of radiotherapy on the survival of cervical cancer patients. In their analysis based on the SEER database, the study revealed varying responses among cervical cancer patients to radiotherapy. Notably, the survival rates of patients who underwent both surgery and radiotherapy were found to be relatively low. When applying radiotherapy to cervical cancer patients, the study emphasizes the importance of considering multiple clinical features. These include age, tumor size, and TNM stage. The study found that external beam radiation alone is less effective compared to the outcomes achieved with combined radiotherapy in the treatment of cervical cancer. These findings underscore the complexity of cervical cancer treatment and highlight the need for other therapeutic strategies in order to improve patient outcomes.

Burmeister et al. (2022) conducted a thorough examination of the challenges presented by cervical cancer, with a specific focus on the difficulties faced by low-and middle-income countries. The authors explored alternative therapeutic approaches for cervical cancer, delving into areas such as targeted therapy and immunotherapy. They highlighted the significant drawbacks of current treatment options, which are characterized by debilitating side effects and the emergence of drug resistance. Despite notable progress in combining various therapeutic strategies, there exists an urgent and compelling demand for novel and enhanced treatments. This underscores the critical need for innovative approaches to address the limitations of existing therapies and provide more effective solutions for cervical cancer patients, particularly in resource constrained settings. Eifel (2006) likely discussed the concurrent use of chemotherapy and radiation therapy as the established standard of care for cervical cancer. This combination treatment is often employed to enhance therapeutic efficacy, addressing both local and systemic aspects of the disease. Vora and Gupta (2018) conducted an in-depth analysis of targeted therapy in cervical cancer. Targeted therapies involve the use of drugs specifically designed to target molecules crucial for cancer cell growth and survival. The primary goal of these therapies is to disrupt specific pathways essential for

cancer progression. The review specifically delves into the exploration of pazopanib and bevacizumab, an anti-angiogenic drug, in conjunction with standard chemotherapy for advanced cervical cancer. Bevacizumab works by inhibiting angiogenesis, disrupting the formation of new blood vessels that are crucial for tumor growth. This comprehensive analysis sheds light on the evolving landscape of targeted therapies in cervical cancer, emphasizing the potential of these approaches to improve treatment outcomes and offer new avenues for effective intervention.

Understanding cervical cancer and staging

The use of epidemiology, etiology, and pathophysiology in cervical cancer is crucial for a comprehensive understanding of the disease, guiding prevention, early detection, and treatment strategies. Epidemiology provides insights into the distribution, patterns, and determinants of cervical cancer at a population level. It identifies high-risk groups, informs screening programs. Cervical cancer is the biggest source of morbidity and motility worldwide, ranking fourth in terms of both incidence and mortality (Bray et al., 2018). Approximately 569,847 new cases were reported in 2018, while 311,365 deaths occurred worldwide (Ribeiro et al., 2015). Women have a lifetime risk of developing cervical cancer of 0.9% in high-income nations and 1.6 in low-income ones. Ever since screening tests were introduced, the incidence of cervical cancer has declined in low-income countries (Sriplung et al., 2014). Etiology looks into the causes and risk factors associated with cervical cancer. It informs targeted interventions, such as HPV vaccination and lifestyle modifications, to reduce the incidence of the disease. Having sex at early age or Age at which one participates in sexual intercourse and too many sexual partners are also an important cause of cervical cancer (Vesco et al., 2011). Prolong use of oral contraceptives for more than 5 years increases the risk of cervical cancer (Muñoz et al., 2003). Life style is also an important factor in causing cervical cancer like, smoking, tobacco chewing , the tobacco byproducts leads to destruction of DNA cells present in cervix this causes immune suppression (Ghebre et al., 2017).

Pathophysiology explores the cellular and molecular changes occurring in cervical cells during the development of cancer. Knowledge of pathophysiology is essential for developing targeted therapies and understanding the mechanisms underlying disease progression. Since the cervix is the main effected part in cervical cancer. Which is also called as the neck of the uterus and protrudes into vagina the internal cavity of the cervix called cervical canal. This canal is divided into 2 sections. They are Endocervix and Ectocervix. Endocervix is the inner part of the cervix that extends into the uterus. It is not visible to the naked eye and is lined with columnar epithelial cells that produce mucus. Ectocervix is the outer part of the cervix that connects to the vagina. It is lined with mature squamous epithelial cells. Both parts meet at the squamocolumnar junction, and changes in this area can be a site for cervical cancer development. The changes that occur in the squamocolumnar junction, also known as the transformation zone, are often related to a process called metaplasia. Metaplasia involves the replacement of one type of cell with others where columnar epithelial cells from the endocervix are replaced by squamous epithelial cells from the ectocervix due to various factors. These changes represent a progression from normal tissue to precancerous conditions and, if not addressed, can eventually lead to invasive cervical cancer. *Figure 1* shows the metaplastic transformation at the squamocolumnar junction.

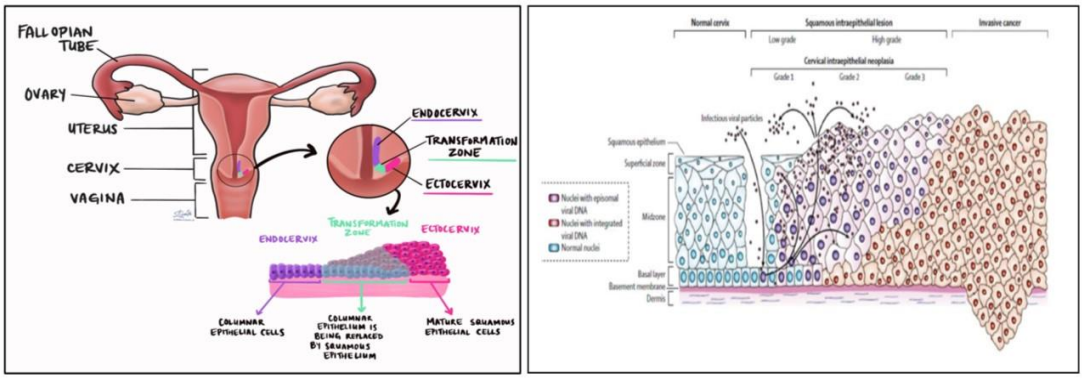

Figure 1. *Development of Metapalsia in the squamocolumnar Juntion.*

Cervical cancer progresses through stages, each indicating the extent of the disease. In the early stages, such as Stage 0 and IA, the cancer is confined to the cervix. As it advances to IB stages, visible lesions may be present, cancer is more extensive but still confined to the cervix. In Stage IIA, Cancer has spread beyond the cervix but not to the pelvic sidewall or lower third of the vagina, Stage IIB Cancer has spread to the pelvic sidewall or lower third of the vagina. In more advanced stages like IIIA and IIIB, cancer may reach the vagina's lower part or the pelvic wall, involves hydronephrosis or causes non-functioning kidney. Stage IVA cancer has spread to adjacent organs, such as the bladder or rectum. The specific stage of cervical cancer is determined through a combination of clinical examination, imaging studies, and sometimes surgical findings. Staging is crucial for treatment planning and prognosis estimation. It is important to note that the specific treatment plan is individualized based on factors such as the patient's overall health, preferences, and the expertise of the medical team. Personalized advice from healthcare professionals, considering the cancer's characteristics and the patient's situation, is crucial. *Figure 2* shows the cervical cancer development and progression along the cervical spectrum.

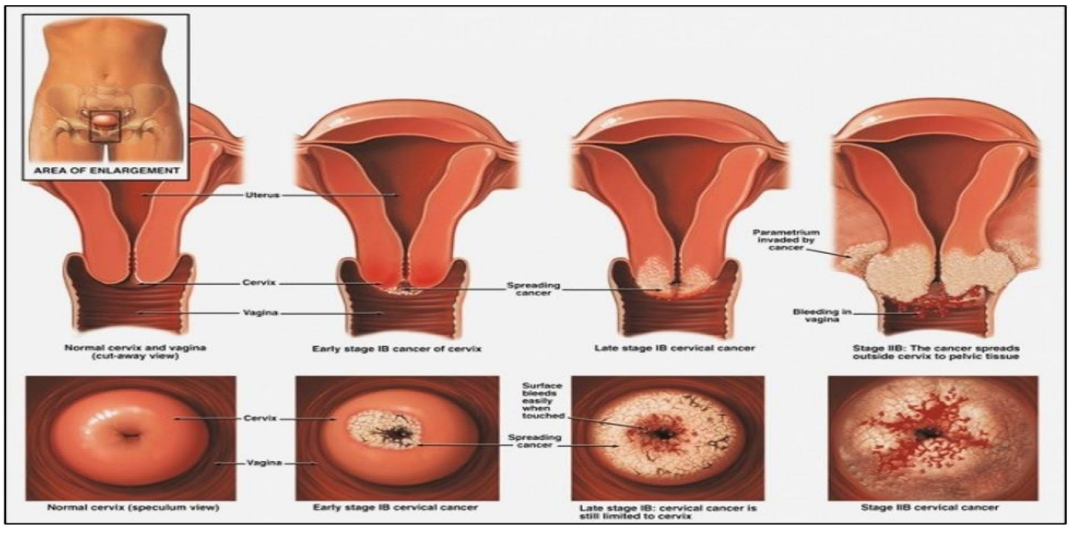

Figure 2. *Evolutions and Progression of Cervical Cancer across Distinct Stages in the Cervix.*

Epidimlogy of cervical cancer

Cervical cancer remains a significant global health challenge, particularly in low-and middle-income countries where access to screening and prevention measures is limited. Understanding the epidemiology of cervical cancer is crucial for developing effective prevention and treatment strategies. Here, we provide an overview of the epidemiological aspects of cervical cancer, including its incidence, mortality, risk factors, and geographic distribution.

Incidence and mortality

Cervical cancer is the fourth most common cancer among women globally, with an estimated 604,127 new cases and 341,831 deaths reported in 2020 (WHO, 2020). The incidence and mortality rates vary widely across regions, with the highest burden observed in sub-Saharan Africa, South Asia, and Latin America. Despite advancements in screening programs and vaccination against human papillomavirus (HPV), cervical cancer remains a leading cause of cancer-related deaths among women in many parts of the world.

Risk factors

Persistent infection with high-risk HPV types, particularly HPV-16 and HPV-18, is the primary risk factor for cervical cancer development. Other factors associated with an increased risk of cervical cancer include early onset of sexual activity, multiple sexual partners, smoking, immune suppression, and lack of access to regular screening and preventive measures. Socioeconomic factors such as poverty, limited education, and inadequate healthcare infrastructure also contribute to the disparity in cervical cancer burden.

Geographic distribution

The distribution of cervical cancer incidence and mortality varies significantly by geographic region and level of economic development. High-income countries with well-established screening programs have seen a decline in cervical cancer incidence and mortality rates over the past few decades. In contrast, low-and middle-income countries, particularly those in sub-Saharan Africa and South Asia, bear the highest burden of cervical cancer, primarily due to limited access to screening, vaccination, and treatment services.

Prevention and control effects

Primary prevention strategies for cervical cancer include HPV vaccination and promotion of safe sexual practices. Secondary prevention involves regular cervical cancer screening, typically through cytology-based Pap smear or HPV DNA testing, followed by appropriate management of precancerous lesions. Despite the availability of effective prevention measures, implementation challenges such as limited healthcare infrastructure, cultural barriers, and resource constraints hinder their widespread adoption in many low-resource settings. Cervical cancer poses a significant public health challenge worldwide, with marked disparities in incidence, mortality, and access to preventive measures. Addressing these disparities requires a multifaceted approach involving vaccination, screening, early detection, and access to timely and affordable treatment services, particularly in underserved populations.

Risk factors of cervical cancer

Human Papilloma Virus (HPV) infection

Human papillomavirus (HPV) infection, particularly with high-risk strains, is the primary risk factor for cervical cancer (Crosbie et al., 2013). Persistent infection with oncogenic HPV types, such as HPV-16 and HPV-18, increases the likelihood of developing cervical dysplasia and carcinoma.

Sexual behavior

Early onset of sexual activity and having multiple sexual partners are significant risk factors for cervical cancer (Bray et al., 2018). These behaviors increase the likelihood of HPV exposure and subsequent cervical cell transformation.

Smoking

Smoking is associated with an increased risk of cervical cancer, independent of HPV infection (Plummer et al., 2016). Tobacco smoke contains carcinogens that can directly damage cervical cells, leading to neoplastic changes.

Immuno supression

Immuno compromised individuals, such as those living with HIV/AIDS or undergoing immunosuppressive therapy, have a higher risk of developing cervical cancer Impaired immune function reduces the body's ability to clear HPV infections and suppresses immune surveillance against precancerous cervical lesions.

Lack of screening and vaccination

Limited access to cervical cancer screening programs and HPV vaccination increases the risk of late-stage diagnosis and progression to cervical cancer (WHO, 2020). Routine screening with Pap smears or HPV testing enables early detection and intervention, reducing cervical cancer incidence and mortality.

Current treatment landscape

Cervical cancer remains a significant global health concern, with an estimated 604,127 new cases and 341,831 deaths worldwide in 2020 alone (WHO, 2020). The landscape of cervical cancer treatment has evolved significantly over the years, with advances in surgery, radiotherapy, chemotherapy, and more recently, targeted therapies. The treatment landscape of cervical cancer continues to evolve with ongoing research, clinical trials, and advancements in precision medicine and immunotherapy. Multidisciplinary care, personalized treatment approaches, and access to comprehensive cancer centers are essential for optimizing outcomes and improving survival rates for patients with cervical cancer. The current treatment landscape of cervical cancer typically involves a combination of surgery, radiotherapy, chemotherapy, and targeted therapy, depending on the stage and characteristics of the disease.

Importance of exploring targeted therapeutic strategies: Surgery, radiotherapy, chemotherapy and targeted therapy

Cervical cancer can be treated by employing a combination of diverse therapeutic strategies, each meticulously selected based on the specific characteristics of the disease and the individual needs of the patient. From Cervical cancer progresses through stages, each are indicating the extent of the disease. In the early stages, such as Stage 0 and IA, the cancer is confined to the cervix. As it advances to IB stages, visible lesions may be present, cancer is more extensive but still confined to the cervix. In Stage IIA, Cancer has spread beyond the cervix but not to the pelvic sidewall or lower third of the vagina, Stage IIB Cancer has spread to the pelvic sidewall or lower third of the vagina. In more advanced stages like IIIA and IIIB, cancer may reach the vagina's lower part or the pelvic wall, involves hydronephrosis or causes non-functioning kidney. Stage IVA cancer has spread to adjacent organs, such as the bladder or rectum. Traditional surgical interventions to advanced radiation therapy techniques, including external beam radiation and brachytherapy. Chemotherapy, utilizing powerful drugs to impede cancer growth, continues to be a fundamental component of treatment, often complementing other modalities. Furthermore, emerging approaches like immunotherapy and targeted therapy offer promising avenues for enhanced efficacy. This section delves into the intricacies of these treatment modalities.

Surgery for cervical cancer

Surgery is a common and effective treatment option for cervical cancer, especially in the early stages. Conization or cone biopsy is one of the surgical treatments used to treat extremely early-stage cervical cancer or discover precancerous abnormalities. In some cases, surgery may be considered after chemoradiation to remove any remaining tumor or to manage recurrent disease. Surgery plays a crucial role in the management of early-stage cervical cancer. The standard surgical approach for localized disease includes radical hysterectomy (*Figure 3*) and pelvic lymphadenectomy (Koh et al., 2019). However, the advent of minimally invasive techniques, such as laparoscopic and robotic-assisted surgery, has offered comparable oncologic outcomes with reduced morbidity compared to traditional open surgery (Ramirez et al., 2018).

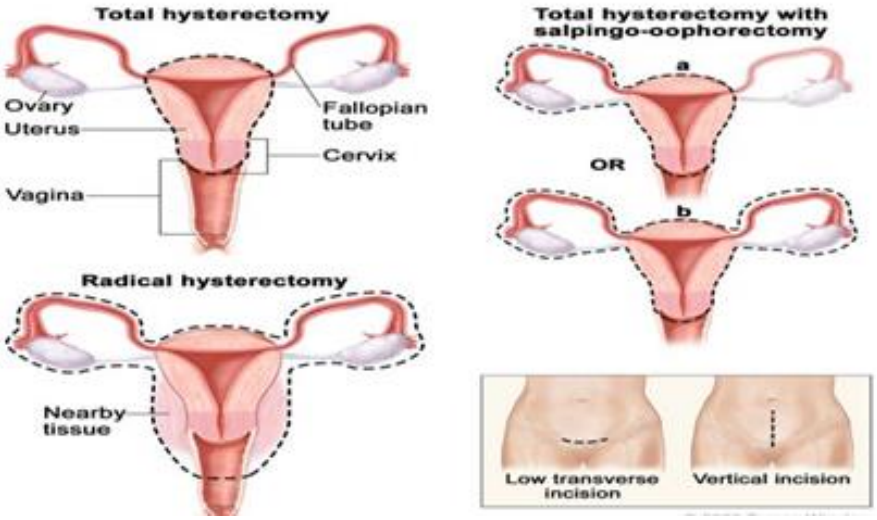

Figure 3. *Representation of total hysterectomy and radical hysterectomy.*

Radiation therapy

Principles and techniques of radiotherapy in cervical cancer treatment

Radiation therapy, often known as radiotherapy, is a localised treatment that use high doses of radiation to target and kill cancer cells. It is a common and effective treatment modality for various cancers, including cervical cancer. It damages the DNA of cancer cells, preventing them from growing and dividing. It shrinks tumors; reduce the size of tumors before surgery or to control the growth of cancer cells. The types of radiation therapy most often used to treat cervical cancer are: External beam radiation, Brachytherapy and combination therapy. External beam radiation therapy (EBRT) and brachytherapy (internal radiation therapy) may be used as adjuvant therapy after surgery or as a primary treatment option for patients who are not surgical candidates (Viswanathan et al., 2012).

External Beam Radiotherapy (EBRT) and brachytherapy: Eddicacy, side effect and outcomes

In External Beam Radiation Therapy (EBRT) the radiation is delivered from outside the body using a machine. It uses high dose radiation to destroy cancerous cells or shrink tumors. EBRT is also typically used in conjunction with chemotherapy (also known as concurrent chemoradiation). The advanced external beam radiotherapy (EBRT) techniques including intensity modulated radiotherapy (IMRT) and volumetric arc therapy (VMAT) are increasingly utilised, with some evidence of side-effect reduction (Hasselle et al., 2011). External beam radiation treatment for cervical cancer may have the following short-term adverse effects include stomach upset, loose stools vomiting, nausea, skin changes (mild redness), fatigue, usually, these adverse effects go better in the weeks after the end of therapy. Brachytherapy, often known as interstitial brachytherapy is a form of radiation therapy that involves the placement of radioactive sources directly into or very close to the tumour (*Figure 4*). Unlike external beam radiation therapy, where radiation is delivered from outside the body, interstitial brachytherapy involves placing radioactive sources directly into the tissues being treated. It is used in the treatment of various cancers, including gynecological cancers such as cervical cancer, prostate cancer, breast cancer, and head and neck cancers. Brachytherapy can be used either alone or in combination with EBRT to increase the dose focally in advanced primary tumors requiring high doses to be cured in cervical cancer (Green et al., 2001). Brachytherapy comes in two varieties: high dose rate brachytherapy and low-dose rate (LDR) brachytherapy. Many of the negative effects of EBRT, including low blood counts, weariness, nausea, diarrhea, and bladder discomfort, can also be caused by brachytherapy. Leg swelling, weakening bones and vaginal stenosis are among the long-term negative effects of radiation therapy (Eifel et al., 2018) (*Table 1*).

Table 1. *Overview of Treatment Modalities of Radiation Therapy*.

Aspect	External beam radiation therapy	Brachytherapy
Definition	Radiation delivered from outside the body using a machine.	Radiation delivered directly inside the body near the tumor.
Treatment Duration	Typically administered daily over several weeks.	Can be administered in a single session (HDR) or over several days (LDR).
Side Effects	Side effects may include fatigue, skin irritation, and gastrointestinal issues.	Side effects may include vaginal irritation, bladder irritation, and bowel irritation.
Combination with other treatments	Often used in combination with brachytherapy and chemotherapy.	Can be used alone or in combination with external beam radiation therapy and chemotherapy.
Monitoring	Patients undergo regular monitoring during treatment.	Patients are monitored during and after treatment for response and side effects.

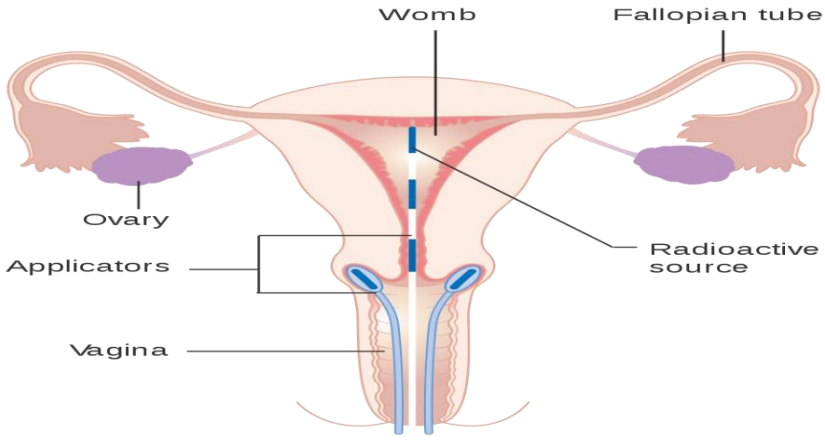

Figure 4. *Placement of radioactive source close to the tumor through the vagina.*

Combining radiotherapy with other modalities for improved outcomes

Combined therapy is a combined use of brachytherapy and external beam radiation therapy to optimize treatment outcomes. Chemotherapy-radiation treatment is a prominent combination technique that includes radiation therapy and chemotherapy. It decreases the size of the tumor, stops micrometastases, and medication resistance, and makes the hypoxic cells in the cervix more radiosensitive when used to treat cervical cancer. Chemotherapy increases the sensitivity of cancer cells to radiation, which can enhance treatment outcomes.

Emerging trends and future persepctives in radiotherapy for cervical cancer

Emerging techniques, such as intensity-modulated radiation therapy (IMRT) and image-guided radiation therapy (IGRT), enable dose escalation to the tumor while sparing surrounding normal tissues, thereby reducing treatment-related toxicities (Choi et al., 2009).

Chemotherapy

Chemotherapy is a treatment in which anti-cancer medications are injected into a vein or administered orally. These medications enter the bloodstream and may reach practically any part of the body, making this treatment effective for eliminating cancer cells throughout the body. Chemo is given in cycles, followed by a rest period to give you time to recover from the effects of the drugs.

Role of chemotherapy in treating cervical cancer management: Neoadjuvant, adjuvant and concurrent

Chemotherapy plays a crucial role in the management of cervical cancer, both as a primary treatment modality and in combination with radiotherapy or surgery. Platinum-based regimens, such as cisplatin and carboplatin, are commonly used in the neoadjuvant, concurrent, and adjuvant settings (Tewari et al., 2014). Platinum-based doublet therapy with concurrent irradiation is the “preferred treatment” and “potentially the best regimen” for stage IB-IVA cervical cancer, For bulky, stage IB2 or locally advanced stage II-IVA cervical cancer, the concurrent chemoradiation with platinum

based chemotherapy is the primary treatment, 35% to 90% of patients are failed to treat alone with radiation therapy (DeVita et al., 2012). For some stages of cervical cancer, concurrent chemoradiation, which combines radiation and chemotherapy, is the recommended treatment. Chemo improves the effectiveness of radiation. And for advanced cases, cisplatin-based chemotherapy has been traditionally used.

Combination chemotherapy approaches and their efficacy

Chemotherapy drugs can be given as singlet therapy, combinational therapy and triplet therapy as seen in *Table 2*. Single Agents: In the NCCN guidelines, cisplatin is strongly recommended as the standard single agent for chemoradiotherapy, and it has been widely used in the comprehensive treatment of cervical cancer; cisplatin was also proven to improve the outcomes in nearly all trials for cervical cancer (Thigpen et al., 1981). Combination Chemotherapy: Recent studies have demonstrated that combination neoadjuvant chemotherapy with paclitaxel (PTX) and cisplatin (DDP) can reduce tumor volume and improve the operative rate with low toxicity, meaning that this therapeutic schedule can improve the long-term survival of patients with cervical cancer (McCormack et al., 2013; Park et al., 2009). Triplet Chemotherapy: A randomized phase II study of cisplatin and ifosfamide with or without paclitaxel demonstrated increased activity with the triple drug combination (*Table 3*).

***Table 2**. Overview of Treatment Modalities for Chemotherapy.*

Single tagent chemotherapy	Combination chemotherapy	Triplet chemotherapy
Cisplatin	Cisplatin and topotecan	Older cisplatin combinations: Methotrexate, vinblastine, doxorubicin, and cisplatin
Vinorelbine	Cisplatin and gemcitabine	Older cisplatin combinations: Bleomycin, vindesine, mitomycin-C, and cisplatin
Irinotecan	Cisplatin and vinorelbine	Older cisplatin combinations:Methotrexate, vinblastine, doxorubicin, and cisplatin
Paclitaxel	Cisplatin and irinotecan	Carboplatin combination: Bleomycin, ifosfamide, and carboplatin
Pemetrexed	Cisplatin and paclitaxel	Paclitaxel combinations: Ifosfamide, paclitaxel, and cisplatin
Ifosfamide	Cisplatin and mitomycin-C	-
Topotecan	Cisplatin and ifosfamide	-
Capecitabine	Cisplatin and decitabine	-

***Table 3**. Overview of Treatment Modalities for different stages of Cervical Cancer.*

Stage	Area affected	Surgery	Radiation therapy	Chemotherapy	Targeted therapy
0	Epithelium	Surgical (Conization)	-	-	-
IA1	Cervical Invasive	Surgical (Conization)	-	-	-
IA2	Cervical Invasive	Surgical (Conization)	-	-	-
IB1	Visible Lesion	Surgical or Radiotherapeutic	Concurrent Chemoradiation	Yes	Yes
IB2	Visible Lesion	Multidisciplinary Treatment	Concurrent Chemoradiation	Yes	Yes
IB3	Visible Lesion	Pelvic Lymph Node Dissection	Concurrent Chemoradiation	Yes	Yes
IIA	Upper 2/3 of Vagina	Surgical or Radio therapeutic	Concurrent Chemoradiation	Yes	Yes
IIB	Para metrial Invasion	Multidisciplinary Treatment	Concurrent Chemoradiation	Yes	Yes
IIIA	Lower 1/3 of Vagina	Multidisciplinary Treatment	Concurrent Chemoradiation	Yes	Yes
IIIB	Pelvic Wall/Hydronephrosis	Multidisciplinary Treatment	Concurrent Chemoradiation	Yes	Yes

IVA	Beyond Pelvis	Multidisciplinary Treatment	Concurrent Chemoradiation	Yes	Yes
IVB	Distant Spread	Multidisciplinary Treatment	Medical Treatment	Yes	Yes

Targeted therapy

Targeted drug therapy is the use of medications that target or direct at proteins on cervical cancer cells that aid in their growth, dissemination, or survival.

Mechanism of targeted therapy in cervical cancer

Targeted drugs function by killing or slowing the development of cancer cells. This novel therapeutics attack to regulate these signal transduction pathways by blocking the extracellular transmembrane receptors or obstructing the intracellular proteins such as tyrosine kinase. This type novel therapeutic approach is also known as molecular targeting (Markman et al., 2008).

Review of targeted therapies: Tyrosine kinase inhibitor, monoclonal antibodies, vascular endithelial growth factor

Cervical cancer has moderate to high levels of Epidermal Growth Factor Receptor (EGFR) protein expression (Scambia et al., 1998). EGFR inhibitors have been approved for the treatment of various cancers. Currently, EGFR targeted pharmacologically in two different ways: inhibitors of the EGFR tyrosine kinase and anti-EGFR monoclonal antibodies. The EGFR tyrosine kinase inhibitor, gefitinib, was ineffective in patients with refractory cervical cancer, although 87% of tumors expressed high levels of EGFR (Goncalves et al., 2008). Cetuximab, a monoclonal antibody against EGFR, was multiple studies with or without cytotoxic chemotherapy have shown no meaningful benefit with this drug (Farley et al., 2011; Santin et al., 2011). Unfortunately, the single agents like gefitinib and erlotinib show minimal effects in the treatment of recurrent cervical cancer (Schilder et al., 2009).

The Vascular Endothelial GrowthFactor (VEGF) pathway is widely recognized as a crucial contributor to angiogenesis, the formation of new blood vessels. Targeting Vascular Endothelial Growth Factor (VEGF) is a key approach in antiangiogenic therapy. Tumor-induced angiogenesis often results in disorganized vasculature, restricting the effective delivery of drugs to cancer cells. Antiangiogenic agents have demonstrated the ability to “normalize” tumor blood vessels, enhancing the delivery of oxygen and drugs to the tumor microatmosphere (Jain, 2005). Elevated VEGF expression is associated with poor prognosis and early recurrence. Bevacizumab, a recombinant humanized monoclonal immunoglobulin (Ig)-G1 antibody targeting VEGF-A, has been used as a single agent in metastatic cervical cancer, showing relatively good tolerance and contributing to progression-free survival (Monk et al., 2009). However, tyrosine kinase inhibitors like sunitinib and pazopanib have not exhibited significant benefits in terms of response rate and progression-free survival in advanced cervical cancer (Mackay et al., 2010). Currently Brivanib, an inhibitor of VEGFR and FGFR, is under evaluation for its role in advanced cervical cancer (Vora and Gupta, 2018).

Clinical trails and studies evaluating targeted therapy efficacy and safety

A significant method for treating a variety of malignancies is targeted therapy. When compared to other cancer types, its application for cervical cancer is currently restricted. However, the promise of targeted medicines in the treatment of cervical cancer is being investigated through continuing research and clinical trials. The safety and effectiveness of targeted medicines, both alone and in combination with other treatments, are still being studied in clinical trials.

Combination therapies and multimodal approaches

Rational for combining targeted therapy, radiotherapy and chemotherapy

In addition to these multidisciplinary treatments may involve a combination of surgery, radiation therapy, chemotherapy, and other targeted therapies, depending on the characteristics of the cervical cancer and the stage of its progression. This approach aims to optimize treatment outcomes while minimizing side effects and improving the overall quality of care for the patient. Bevacizumab, for instance, has been studied in conjunction with chemotherapy for advanced cervical cancer and has demonstrated an improvement in overall survival.

Future directions and challenges

Promising avenues for further research and development

Many ongoing clinical trials are exploring novel therapeutic approaches, including targeted therapies, immunotherapies, and combination regimens, to improve outcomes for patients with advanced or recurrent disease. Research on preventing cervical cancer, which led to the approval of Gardasil and Cervarix, showed that the vaccinations are almost 100% effective in preventing cervical dysplasia brought on by HPV types 16 and 18, as well as recurrent infections of the cervical mucosa. According to recent research, Gardasil provides protection against the targeted HPV genotypes for at least 10 years, Cervarix for at least 9 years, and Gardasil for at least 6 years. The microencapsulation of DNA vaccines is an additional delivery method that has been examined in several clinical studies.

Addressing treatment resistance and disease recurrence

Resistance to therapy and disease recurrence in cervical cancer can be caused by a variety of reasons. Understanding and treating these issues are critical to improving patient outcomes. Recurrence of cervical cancer is recorded in 10-20% of early-stage patients following surgery or radiation, and up to 70% of locally advanced-stage patients (Gadducci et al., 2010). Resistance to cisplatin may primarily result from decreased intracellular cisplatin accumulation. Reduced intracellular cisplatin accumulation leads to decreased cisplatin-DNA adduct formation, which in turn causes resistance to cisplatin. These factors include decreased uptake, increased efflux, and inactivation by thiol-containing proteins (Shen et al., 2012).

Ethical considerations and patient-centered care in cervical cancer treatment

Palliative care plays a crucial role in managing symptoms and improving quality of life for patients with advanced or metastatic cervical cancer. This may involve pain management, supportive care, and psychological support for patients and their families. The treatment landscape of cervical cancer continues to evolve rapidly, with ongoing

efforts to optimize therapeutic strategies and improve patient outcomes. Multimodal approaches integrating surgery, radiotherapy, chemotherapy, and targeted therapies hold promise in achieving better control of the disease and reducing treatment-related morbidities. However, challenges such as treatment resistance, disease recurrence, and access to advanced therapies remain areas of active research and clinical investigation.

Case studies

In this section, we present case studies that provide insights into the application of different therapeutic modalities for cervical cancer treatment and their impact on patient outcomes.

Case 1: Targeted HDR-ISBT approach for locally advanced cervical cancer

Patient Background: A 54-year-old female presented with irregular genital bleeding and a notable weight loss of 13 kg over the course of a year. Upon examination at another hospital, she was diagnosed with cervical cancer, characterized by a substantial primary tumor with a transverse diameter of 10.5 cm. Further analysis revealed cervical clear cell carcinoma and bilateral parametrial infiltration. *Treatment Modalities*: The initial phase of treatment involved irradiation of the whole pelvis and para-aortic lymph node, delivering a total of 50 Gy in 25 fractions through the 2 opposed-fields technique external beam radiation therapy. Despite this, the tumor exhibited only a marginal reduction in size to 8.9 cm. Subsequently, the patient underwent highdose-rate interstitial brachytherapy (HDR-ISBT) in a phased approach. The first HDR-ISBT was administered without the "intentional internal high-dose (IIHD) policy." Recognizing the rectum dose limitation, the following two HDR-ISBT sessions employed the "IIHD policy." This technique involved administering high doses selectively to the interior of the tumor. Needle insertion was maintained until the completion of the third HDR-ISBT session, with careful monitoring via simulation computed tomography and magnetic resonance imaging after each session to validate needle placement and assess dose distribution. *Outcome*: The treatment approach yielded a complete response, with no recurrence during the 2 years and 9 months of follow-up. No acute adverse events related to needle insertion or the IIHD HDR-ISBT technique was reported. This case introduces a targeted HDR-ISBT strategy as a promising and safe solution for locally advanced, bulky cervical cancer, as documented in the article by Kashihara et al. (2020) titled" A case report of a patient with bulky uterine cervical neoplasm who achieved complete response with 'intentional internal high-dose policy' high-dose-rate interstitial brachytherapy" published in Medicine.

Case 2: IB3 cervical cancer in pregnancy: A successful approach with neoadjuvant chemothera[y and radical surgery

Patient Background: A 36-year-old pregnant woman presented with a diagnosis of a 5-cm-diameter stage IB3 squamous cell carcinoma of the uterine cervix at 13 gestational weeks. The cancer was characterized as invasive nonkeratinizing squamous cell carcinoma, with positive human papilloma virus (HPV) 18 status, and staged as IB3 following the 2018 International Federation of Gynecology and Obstetrics (FIGO) classification. Despite the diagnosis, the patient expressed a strong desire to preserve the pregnancy and declined immediate surgery. *Treatment Modalities*: The Multidisciplinary Team (MDT) recommended a neoadjuvant chemotherapy (NACT)

approach with carboplatin and paclitaxel. Over a span of 20 to 32 gestational weeks, the patient underwent five courses of chemotherapy. In collaboration with the MDT, fetal lung maturity was carefully achieved by the 35th week. Subsequently, a caesarean section was performed, followed by radical hysterectomy and pelvic lymphadenectomy. The chemotherapy regimen included paclitaxel (175 mg/mq every 21 days) and carboplatin (AUC=5 on day 1 every 21 days). Throughout the treatment process, monitoring encompassed fetal and maternal Doppler readings, amniocentesis, and a comprehensive assessment of fetal and maternal well-being. *Outcome*: The caesarean section resulted in the successful delivery of a healthy female infant weighing 2060 g, with Apgar scores of 9 and 10 at 1 and 5 minutes, respectively. Following the caesarean section, radical hysterectomy and pelvic lymphadenectomy were performed, revealing a 3.5 cm identifiable lesion. Histological examination indicated a poorly differentiated cervical adenocarcinoma with local adenosquamous carcinoma features. Postoperative radiotherapy was proposed as part of the ongoing treatment plan. Both the mother and the infant were discharged in good general condition, and at the last follow-up, which occurred 4 months post-surgery, both individuals remained in good health. Importantly, no metastasis of maternal malignancy was detected in the placenta and umbilical cord upon extensive pathological examination. This information presented here is derived from a documented case study published in the article titled 'A case of successful maintained pregnancy after neoadjuvant chemotherapy plus radical surgery for stage IB3 cervical cancer diagnosed at 13 weeks,' authored by Guo et al., (2020).

Conclusion

Cervical cancer presents a significant global health challenge; however, considerable progress has been made in comprehending and managing this disease. Efforts in prevention, early detection, and treatment have contributed to improved outcomes and reduced mortality rates. In these study different therapeutic strategies, including surgery, radiation therapy, chemotherapy, and targeted therapy, is discussed in detail in order to provide insights to the future work. The choice of treatment depends on the stage of cancer, the patient's overall health, and other individual factors. However the optimal management of cervical cancer often involves a combination of treatments, known as a multidisciplinary approach. Future research will focus on refining targeted therapies, exploring novel treatment combinations, and addressing the challenges faced by many women.

Acknowledgement

This research is self-funded.

Conflict of interest

The authors confirm that there is no conflict of interest involve with any parties in this research study.

REFERENCES

[1] Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R.L., Torre, L.A., Jemal, A. (2018): Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. – CA: A Cancer Journal for Clinicians 68(6): 394-424.

[2] Burmeister, C.A., Khan, S.F., Schäfer, G., Mbatani, N., Adams, T., Moodley, J., Prince, S. (2022): Cervical cancer therapies: Current challenges and future perspectives. – Tumour Virus Research 13: 14p.

[3] Choi, C.W., Cho, C.K., Yoo, S.Y., Kim, M.S., Yang, K.M., Yoo, H.J., Seo, Y.S., Kang, J.K., Lee, D.H., Lee, K.H., Lee, E.D. (2009): Image-guided stereotactic body radiation therapy in patients with isolated para-aortic lymph node metastases from uterine cervical and corpus cancer. – International Journal of Radiation Oncology* Biology* Physics 74(1): 147-153.

[4] Crosbie, E.J., Einstein, M.H., Franceschi, S., Kitchener, H.C. (2013): Human papillomavirus and cervical cancer. – Lancet [Internet] 382: 889-999.

[5] DeVita, V.T., Lawrence, T.S., Rosenberg, S.A. (2012): Cancer: principles & practice of oncology: primer of the molecular biology of cancer. – Lippincott Williams & Wilkins 2374p.

[6] Eifel, P.J. (2006): Concurrent chemotherapy and radiation therapy as the standard of care for cervical cancer. – Nature Clinical Practice Oncology 3(5): 248-255.

[7] Eifel, P.J., Klopp, A.H., Berek, J.S., Konstantinopoulos, P.A. (2018): Cancer of the cervix, vagina, and vulva. – In DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology. – Wolters Kluwer Health Pharma Solutions (Europe) Ltd. 38p.

[8] Farley, J., Sill, M.W., Birrer, M., Walker, J., Schilder, R.J., Thigpen, J.T., Coleman, R.L., Miller, B.E., Rose, P.G., Lankes, H.A. (2011): Phase II study of cisplatin plus cetuximab in advanced, recurrent, and previously treated cancers of the cervix and evaluation of epidermal growth factor receptor immunohistochemical expression: a Gynecologic Oncology Group study. – Gynecologic Oncology 121(2): 303-308.

[9] Gadducci, A., Tana, R., Cosio, S., Cionini, L. (2010): Treatment options in recurrent cervical cancer. – Oncology Letters 1(1): 3-11.

[10] Ghebre, R.G., Grover, S., Xu, M.J., Chuang, L.T., Simonds, H. (2017): Cervical cancer control in HIV-infected women: past, present and future. – Gynecologic Oncology Reports 21: 101-108.

[11] Goncalves, A., Fabbro, M., Lhommé, C., Gladieff, L., Extra, J.M., Floquet, A., Chaigneau, L., Carrasco, A.T., Viens, P. (2008): A phase II trial to evaluate gefitinib as second-or third-line treatment in patients with recurring locoregionally advanced or metastatic cervical cancer. – Gynecologic Oncology 108(1): 42-46.

[12] Green, J.A., Kirwan, J.M., Tierney, J.F., Symonds, P., Fresco, L., Collingwood, M., Williams, C.J. (2001): Survival and recurrence after concomitant chemotherapy and radiotherapy for cancer of the uterine cervix: a systematic review and meta-analysis. – The Lancet 358(9284): 781-786.

[13] Guo, Y., Zhang, D., Li, Y., Wang, Y. (2020): A case of successful maintained pregnancy after neoadjuvant chemotherapy plus radical surgery for stage IB3 cervical cancer diagnosed at 13 weeks. – BMC Pregnancy and Childbirth 20: 1-4.

[14] Hasselle, M.D., Rose, B.S., Kochanski, J.D., Nath, S.K., Bafana, R., Yashar, C.M., Hasan, Y., Roeske, J.C., Mundt, A.J., Mell, L.K. (2011): Clinical outcomes of intensity-modulated pelvic radiation therapy for carcinoma of the cervix. – International Journal of Radiation Oncology* Biology* Physics 80(5): 1436-1445.

[15] Jain, R.K. (2005): Normalization of tumor vasculature: an emerging concept in antiangiogenic therapy. – Science 307(5706): 58-62.

[16] Kashihara, T., Kobayashi, K., Iijima, K., Murakami, N., Yoshida, K., Okuma, K., Nakamura, S., Takahashi, K., Inaba, K., Igaki, H., Nakayama, Y. (2020): A case report of a patient with bulky uterine cervical neoplasm who achieved complete response with "intentional internal high-dose policy" high-dose-rate interstitial brachytherapy. – Medicine 99(27): 4p.

[17] Koh, W.J., Abu-Rustum, N.R., Bean, S., Bradley, K., Campos, S.M., Cho, K.R., Chon, H.S., Chu, C., Clark, R., Cohn, D., Crispens, M.A. (2019): Cervical cancer, version 3.2019, NCCN clinical practice guidelines in oncology. – Journal of the National Comprehensive Cancer Network 17(1): 64-84.

[18] Mackay, H.J., Tinker, A., Winquist, E., Thomas, G., Swenerton, K., Oza, A., Sederias, J., Ivy, P., Eisenhauer, E.A. (2010): A phase II study of sunitinib in patients with locally advanced or metastatic cervical carcinoma: NCIC CTG Trial IND. 184. – Gynecologic Oncology 116(2): 163-167.

[19] Markman, M. (2008): The promise and perils of 'targeted therapy'of advanced ovarian cancer. – Oncology 74(1-2): 1-6.

[20] McCormack, M., Kadalayil, L., Hackshaw, A., Hall-Craggs, M.A., Symonds, R.P., Warwick, V., Simonds, H., Fernando, I., Hammond, M., James, L., Feeney, A. (2013): A phase II study of weekly neoadjuvant chemotherapy followed by radical chemoradiation for locally advanced cervical cancer. – British Journal of Cancer 108(12): 2464-2469.

[21] Monk, B.J., Sill, M.W., Burger, R.A., Gray, H.J., Buekers, T.E., Roman, L.D. (2009): Phase II trial of bevacizumab in the treatment of persistent or recurrent squamous cell carcinoma of the cervix: a gynecologic oncology group study. – Journal of Clinical Oncology 27(7): 1069-1074.

[22] Muñoz, N., Bosch, F.X., De Sanjosé, S., Herrero, R., Castellsagué, X., Shah, K.V., Snijders, P.J., Meijer, C.J. (2003): Epidemiologic classification of human papillomavirus types associated with cervical cancer. – New England Journal of Medicine 348(6): 518-527.

[23] Park, D.C., Suh, M.J., Yeo, S.G. (2009): Neoadjuvant paclitaxel and cisplatin in uterine cervical cancer: long-term results. – International Journal of Gynecologic Cancer 19(5): 943-947.

[24] Plummer, M., de Martel, C., Vignat, J., Ferlay, J., Bray, F., Franceschi, S. (2016): Global burden of cancers attributable to infections in 2012: a synthetic analysis. – The Lancet Global Health 4(9): e609-e616.

[25] Ramirez, P.T., Frumovitz, M., Pareja, R., Lopez, A., Vieira, M., Ribeiro, R., Buda, A., Yan, X., Shuzhong, Y., Chetty, N., Isla, D. (2018): Minimally invasive versus abdominal radical hysterectomy for cervical cancer. – New England Journal of Medicine 379(20): 1895-1904.

[26] Ribeiro, A.A., Costa, M.C., Alves, R.R.F., Villa, L.L., Saddi, V.A., Carneiro, M.A.D.S., Zeferino, L.C., Rabelo-Santos, S.H. (2015): HPV infection and cervical neoplasia: associated risk factors. – Infectious Agents and Cancer 10: 1-7.

[27] Santin, A.D., Sill, M.W., McMeekin, D.S., Leitao Jr, M.M., Brown, J., Sutton, G.P., Van Le, L., Griffin, P., Boardman, C.H. (2011): Phase II trial of cetuximab in the treatment of persistent or recurrent squamous or non-squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. – Gynecologic Oncology 122(3): 495-500.

[28] Scambia, G., Ferrandina, G., Distefano, M., D'Agostino, G., Benedetti-Panici, P., Mancuso, S. (1998): Epidermal growth factor receptor (EGFR) is not related to the prognosis of cervical cancer. – Cancer Letters 123(2): 135-139.

[29] Schilder, R.J., Sill, M.W., Lee, Y.C., Mannel, R. (2009): A phase II trial of erlotinib in recurrent squamous cell carcinoma of the cervix: a Gynecologic Oncology Group Study. – International Journal of Gynecologic Cancer 19(5): 929-933.

[30] Shen, D.W., Pouliot, L.M., Hall, M.D., Gottesman, M.M. (2012): Cisplatin resistance: a cellular self-defense mechanism resulting from multiple epigenetic and genetic changes. – Pharmacological Reviews 64(3): 706-721.

[31] Sriplung, H., Singkham, P., Iamsirithaworn, S., Jiraphongsa, C., Bilheem, S. (2014): Success of a cervical cancer screening program: trends in incidence in songkhla, southern Thailand, 1989-2010, and prediction of future incidences to 2030. – Asian Pacific Journal of Cancer Prevention 15(22): 10003-10008.

[32] Tewari, K.S., Sill, M.W., Long III, H.J., Penson, R.T., Huang, H., Ramondetta, L.M., Landrum, L.M., Oaknin, A., Reid, T.J., Leitao, M.M., Michael, H.E. (2014): Improved survival with bevacizumab in advanced cervical cancer. – New England Journal of Medicine 370(8): 734-743.
[33] Thigpen, T., Shingleton, H., Homesley, H., Lagasse, L., Blessing, J. (1981): Cis-platinum in treatment of advanced or recurrent squamous cell carcinoma of the cervix: a phase II study of the Gynecologic Oncology Group. – Cancer 48(4): 899-903.
[34] Vesco, K.K., Whitlock, E.P., Eder, M., Burda, B.U., Senger, C.A., Lutz, K. (2011): Risk factors and other epidemiologic considerations for cervical cancer screening: a narrative review for the US Preventive Services Task Force. – Annals of Internal Medicine 155(10): 698-705.
[35] Viswanathan, A.N., Moughan, J., Small, W., Levenback, C., Iyer, R., Hymes, S., Dicker, A.P., Miller, B., Erickson, B., Gaffney, D.K. (2012): The quality of cervical cancer brachytherapy implantation and the impact on local recurrence and disease-free survival in radiation therapy oncology group prospective trials 0116 and 0128. – International Journal of Gynecologic Cancer 22(1): 659-664.
[36] Vora, C., Gupta, S. (2018): Targeted therapy in cervical cancer. – ESMO Open 3: 8p.
[37] Yang, J., Cai, H., Xiao, Z.X., Wang, H., Yang, P. (2019): Effect of radiotherapy on the survival of cervical cancer patients: An analysis based on SEER database. – Medicine 98(30): 10p.
[38] World Health Organization (WHO)(2020): Cervical cancer. – WHO Web Portal 6p.