Send Orders for Reprints to reprints@benthamscience.net

Current Medicinal Chemistry, **XXXX**, *XX*, **1-00** **1**

REVIEW ARTICLE

Surgical Advancements, Immunotherapy, Targeted and Conventional Therapies, Biopsy, Colposcopy, and Pap Smear Integration in the Management of Cervical Cancer

Siddhi Wargantiwar[1], Sankha Bhattacharya[1,*] and Abhishek Kanugo[2,*]

[1]*Department of Pharmaceutics, School of Pharmacy & Technology Management, SVKM'S NMIMS Deemed-to-be University, Shirpur, Maharashtra, 425405, India;* [2]*Department of Pharmaceutical Quality Assurance, SVKM Institute of Pharmacy, Dhule, 424001, India*

ARTICLE HISTORY

Received: June 14, 2024
Revised: October 21, 2024
Accepted: October 29, 2024

DOI:
10.2174/0109298673337745241123054840

Abstract: Cervical cancer remains a significant global health concern, making it essential to investigate new treatment options continuously. This page provides an overview of the latest advancements and best practices in detection and intervention, including Pap smears, colposcopy, biopsy, immunotherapy, targeted therapies, chemotherapy, radiation therapy, and surgery. Surgical techniques such as radical hysterectomy and minimally invasive procedures have advanced to enhance patient outcomes and quality of life. Simultaneously, radiation therapy methods have been refined to maximize tumour control while reducing adverse effects. Chemotherapy remains vital, with new drugs and combination regimens demonstrating improved tolerance and efficacy. Immunotherapy, notably immune checkpoint inhibitors, has shown promise in advanced stages of cervical cancer. Additionally, targeted therapies that focus on specific biochemical pathways offer the potential for personalized treatment approaches. This review critically assesses ongoing research, evaluates existing data, and emphasizes the opportunities and challenges of each therapeutic approach. Ultimately, integrating these diverse treatment strategies is the key to enhancing patient outcomes.

Keywords: Cervical cancer, pap smear test, colposcopy, chemotherapy, immunotherapy, targeted therapy.

1. INTRODUCTION

The ongoing, unchecked multiplication of cancer cells is the basic defect that leads to the development of cancer. Cancer cells proliferate and divide uncontrollably, infecting healthy tissues and organs, and eventually spreading throughout the body. They do this instead of adequately reacting to the signals that regulate normal cell behavior [1]. As a result of accumulating aberrations in numerous cell regulatory systems, cancer cells demonstrate a generalized loss of growth control that is reflected in several behaviors that set them apart from normal cells [2].

One of the most often diagnosed gynecologic malignant neoplasms in women worldwide is cervical cancer [3]. Despite significant advancements in preventive measures like the Human Papillomavirus (HPV) vaccination, cervical cancer remains the fourth most common malignancy, causing 342,000 deaths annually [4]. This sobering fact highlights the continuous requirement for a multifaceted strategy that includes efficient screening, precise diagnosis, and customized treatment plans [5].

Cancer that originates in the cervix or any layer of the cervix wall is referred to as cervical cancer. It results from the aberrant proliferation of cells that can infiltrate or spread to different areas of the body as shown in Fig. (**1**). After breast cancer, cervical cancer is the second most common malignancy-related cause of death in women. This cancer develops very slowly [6]. Human papillomavirus (HPV) infection is a required cause of cervical cancer [7]. It is spread by sexual contact, involves infection with several types of viruses, and is dependent on personal hygiene [8]. Most invasive cervical cancers are linked to chronic infections with high-risk HPV strains (such as HPV 16, 18, 31, 33, 52, and 58). However, not all infected women develop cancer, suggesting that environmental and

*Address correspondence to these authors at the Department of Pharmaceutics, School of Pharmacy & Technology Management, SVKM'S NMIMS Deemed-to-be University, Shirpur, Maharashtra, 425405, India; E-mail: sankhabhatt@gmail.com;
Department of Pharmaceutical Quality Assurance, SVKM Institute of Pharmacy, Dhule, 424001, India;
E-mail: abhi.kanugo09@gmail.com

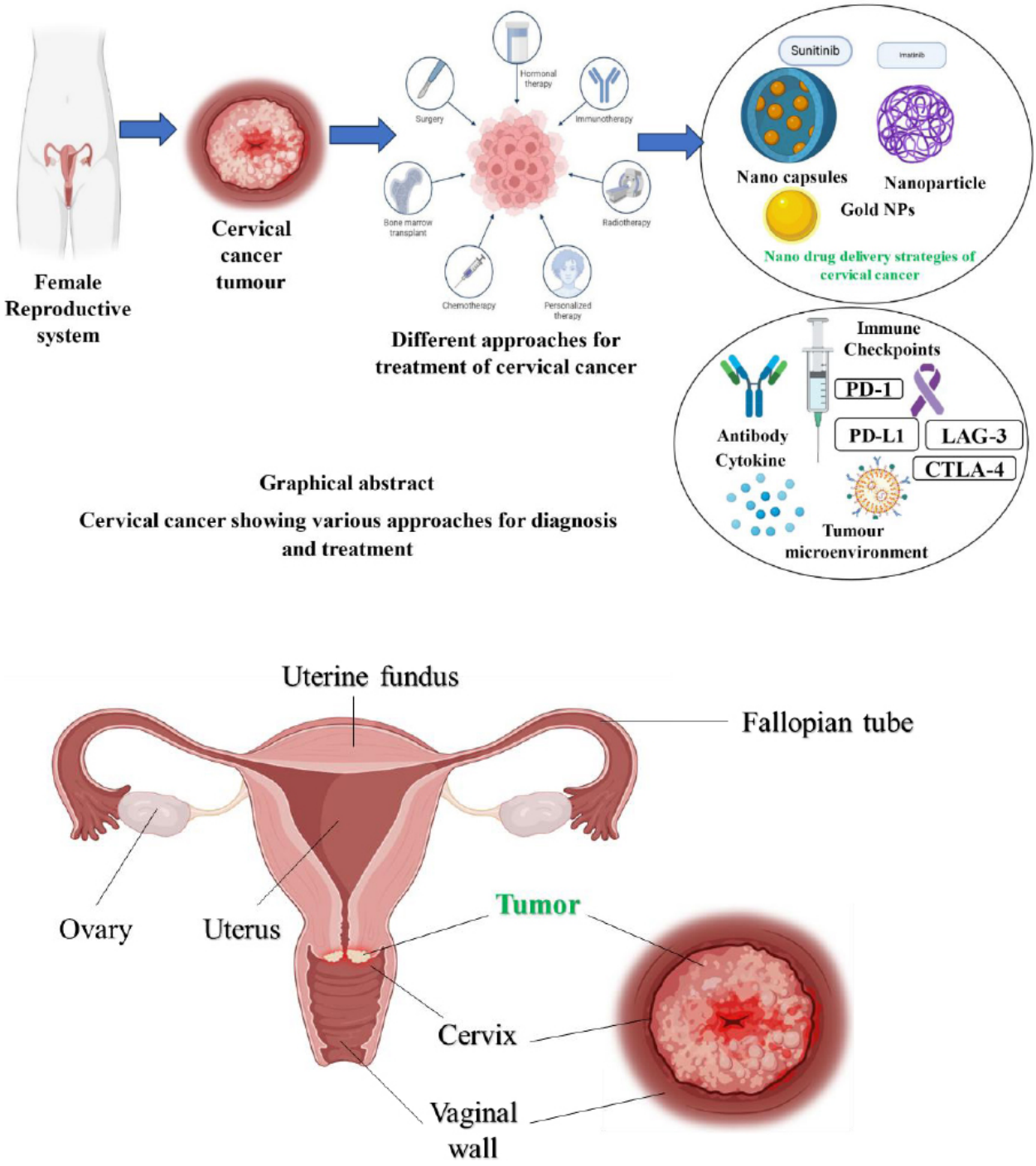

Fig. (1). Anatomy and Tumour Visualisation to Help Understand Cervical Cancer. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

lifestyle factors, along with genetic predispositions, contribute to persistent infections, failure to clear the virus, and tumor development [4]. HPV, a common virus that can be transmitted from one person to another during intercourse, is the cause of almost all cervical malignancies. The HPV comes in a variety of forms. While some HPV types might cause genital or skin warts, others can alter your cervix over time and increase your risk of developing cervical cancer [9]. Since HPV is so widespread, most people will contract

it at some point in their lives. HPV typically has no symptoms; therefore, you are unable to detect your infection. The majority of people will get rid of HPV on their own, but if not, there's a potential that it could eventually lead to cervical cancer [3]. The risk of developing infection from high-risk HPV types is higher in women with HIV [10]. In rural Uganda, nearly 18% of women are affected by high-risk genital HPV infections, which significantly increases their chances of developing cervical cancer. Due to Uganda's low uptake of HPV vaccinations, screening remains a key strategy in combating cervical cancer. Traditional chemotherapy drugs often lack specificity, causing damage to both cancerous and healthy cells. In contrast, targeted therapy represents a shift in approach by focusing on specific molecular changes in cancer cells. In cervical cancer, these changes may include mutations in genes critical for cell growth and proliferation, such as EGFR and HER2 [11]. According to Tewari KS *et al,* Bevacizumab is an instance of a targeted treatment medication that specifically targets the vascular endothelial growth factor (VEGF) pathway. Tumour growth and spread are inhibited by bevacizumab, which interferes with the process of VEGF-promoting blood vessel creation that supplies nutrients to tumours [12]. Compared to conventional chemotherapy, this personalized approach may result in fewer side effects while enhancing treatment efficacy. Another promising treatment avenue for cervical cancer is immunotherapy, which works by activating the body's immune system to target and destroy cancer cells. One of the most effective strategies in immunotherapy is immune checkpoint inhibition. These drugs block the proteins that usually prevent the immune system from attacking healthy cells, thereby allowing a strong anti-tumour immune response by bypassing these immune checkpoints [13].

2. STAGES OF CERVICAL CANCER

There are 3 stages of cervical cancer: early, locally advanced, and metastatic, as mentioned in Fig. (**2**).

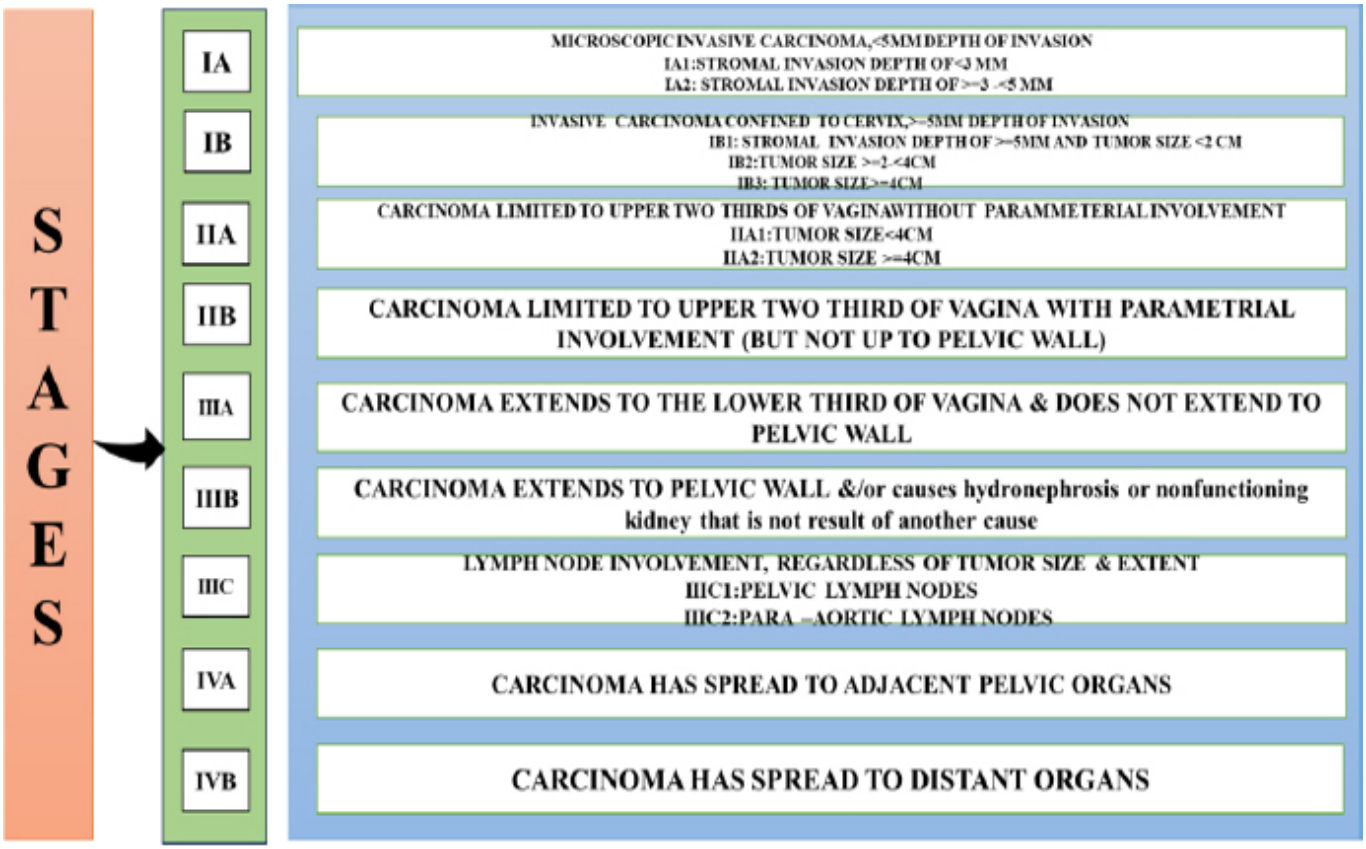

Fig. (2). According to the FIGO classification, cervical cancer progresses from microscopic to advanced stages. One often used classification scheme for cervical cancer stage is the FIGO classification system. From IA, the earliest stage in which the cancer is only microscopically invasive, to IVB, the most advanced stage in which the cancer has spread to distant organs, there are other stages in between. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

2.1. Stage I

Two substages of stage I illness exist, both limited to the cervix. Stage IA is also known as microinvasive illness, meaning that it is not detectable on an MRI, while stage IB is a quantifiable disease that may show up on an MRI [14, 15].

2.1.1. Stage IA: Microinvasive Disease with the Deepest Invasion Less than or Equal to 5mm

Both a transverse dimension and the depth of invasion were used to characterize stage IA illness. Due to the possibility of artifactual mistakes, the transverse dimension is no longer used [15]. Diseases with a depth of 3 mm or less are classified as stage IA1, while those with a depth greater than 3 mm but not exceeding 5 mm are classified as stage IA2. As tumours at this stage are not visible on MRI scans, stage IA disease can only be determined through histopathological examination [16]Notwithstanding the extremely low probability of nodal disease at this stage, pelvic MRI is nevertheless carried out upon confirmation of invasive or microinvasive disease to make sure lesions have not been overestimated and to evaluate for skip lesions and nodal metastases. Preinvasive illness, which needs treatment but does not require a pelvic MRI, is described as malignant cells that do not affect the subepithelial layers [17, 18].

2.1.2. Stage IB: Disease Confined to the Cervix with the Deepest Invasion greater than 5mm

At this stage, the disease depth exceeds 5 mm. The stage IB disease subgroup is classified based on the tumour's maximum diameter. Tumours classified as IB1 are suitable for trachelectomy (a fertility-preserving procedure involving cervical excision and uterovaginal anastomosis), provided no other contraindications are present, whereas IB2 tumours typically are not. These new subgroups within stage IB offer more detailed treatment guidelines. According to Matsuo *et al.*, the survival rate for patients with tumours smaller than 2 cm is twice as high as for those with tumours measuring between 2 and 4 cm [19, 20].

2.2. Stage II

When a disease reaches the uterus but does not affect the pelvic sidewall or the lower third of the vagina, it is diagnosed as stage II. Along with the iliac arteries, pelvic ureters, and lateral lymph nodes, the pelvic sidewall is made up of the obturator internus and piriformis muscles.

2.2.1. Stage IIA: Upper Two-Thirds of the Vagina

Tumours less than or equal to 4 cm in maximum diameter (stage IIA1) and those greater than 4 cm (stage IIA2) comprise the two subgroups that make up this stage. Once more, prognostic factors are used to differentiate between tumours that are 4 cm or greater. Tumours less than 4 cm are less likely to recur and to develop nodal metastases than masses bigger than 4 cm. A rim of high T2-weighted signal intensity encircling a tumour that extends from the cervix into the vagina but does not invade it increases the radiologist's confidence that the vagina is not involved. However, in addition to muscle invasion, high T2-weighted signal intensity fluid or inflammation may be present, therefore the vaginal wall should be represented completely in at least two orthogonal planes. It can be difficult to determine if the top two-thirds of the vagina are involved, and MRI results frequently overstate involvement, especially in the vaginal fornices says Otero-García MM [21]. Nonetheless, anaesthesia-assisted examination provides a reliable diagnosis of upper vaginal involvement, and vaginal gel can help with MRI assessment [22].

2.2.2. Stage IIB: Parametrial Invasion

Between the uterus's body and the pelvic sidewall above the ureters, the parametrium is made up of fat, lymphatics, and vessels [23]. On MRI, the normal cervical stroma exhibits low signal intensity on T2-weighted images. Disruption of the cervical stromal ring, whether focal or diffuse and extending through the full thickness with tissue infiltrating the parametrial fat, is a highly sensitive indicator of parametrial invasion. However, if the cervical stroma is completely disrupted but no tumour is visible in the parametrial tissues, the parametrial invasion may still be absent. Nonetheless, MRI cannot entirely rule out the possibility of microscopic disease extension [16].

2.3. Stage III

The tumour's volume and direction of dissemination determine stage II, and stages IIIA and IIIB exhibit no alterations.

2.3.1. Stage IIIA: Lower One-Third of the Vagina

According to an MRI assessment, the lower third of the vagina consists of vaginal tissue that is below the base of the bladder [24]. A sagittal sequence is best suited for evaluating stage IIIA illness, which affects the lower part of the vagina. At T2-weighted imaging, the tumour exhibits restricted diffusion and intermediate signal intensity [25].

2.3.2. Stage IIIB: Pelvic Sidewall Involvement

A kidney that is not working or hydronephrosis may also be seen in stage IIIB illness, which is described as an expansion to the pelvic wall [14]. When the tumour is less than 3 mm from the pelvic wall, imaging can be used to identify invasion of the pelvic sidewall. Hydroureter or hydronephrosis resulting from ureteric invasion serves as an additional marker for stage IIIB illness [26].

2.3.3. Stages IIIC1 and IIIC2: Pelvic and Para-aortic Lymph Node Involvement

Patients with stage IIIC1 disease appear to have a higher 5-year survival rate than those with stage II cancer. The IIIC1 subgroup's local illness heterogeneity is reflected in this increase [27]. Para-aortic nodal involvement can be independently predicted by parametrial invasion and pelvic nodal disease, according to a study by Ayhan *et al.* [28] In addition, although being prognostically unfavourable, nodal involvement extending to the para-aortic chain has been found to have a superior survival rate when compared to other extra pelvic metastases like supraclavicular nodes or metastatic disease (*i.e.*, stage IVB disease) [29].

2.4. Stage IV

Stage IV refers to sickness that has spread to other organs or locations outside of the actual pelvis. This classification is still in effect. Pulmonary, bone and other visceral metastases are among the mucosal involvement in the bladder and rectal regions, as well as the inguinal and supraclavicular lymph nodes.

2.4.1. Stage IVA

Stage IVA cervical cancer occurs when the tumour spreads into the mucosa and lumen, involving the entire thickness of the bladder wall in front or the rectal wall behind. However, it is not classified as stage IVA if the fat layer separating the cervix from the bladder or rectum is lost, or if the tumour crosses the normal low T2-weighted signal of the bladder or bowel serosa without invading the lumen. Still, this surface-level involvement should be communicated to the clinical team for accurate patient counselling. T2-weighted sagittal and axial oblique imaging are the best methods to interpret these results [30].

2.4.2. Stage IVB

This stage delineates metastases to distant organs, which can occur *via* lymphatic dissemination to farther-reaching lymph node groups, such as the supraclavicular and inguinal areas, or, less frequently, through hematogenous dissemination to the lungs and bones. AIDS-causing viruses, such as HIV, or other illnesses that impair the immune system's ability to fight off illnesses and tobacco use are some factors that can raise your risk of cervical cancer being infected with HIV [31].

3. TYPES OF CERVICAL CANCER

Cervical adenocarcinomas arise within the endocervix's glandular cells whereas squamous cell carcinoma develops from the cells in the ectocervix. An uncommon kind of cervical adenocarcinoma is known as clear-cell adenocarcinoma, sometimes known as clear cell carcinoma or mesonephroma [32, 33]. Adenosquamous Carcinoma appears that adenosquamous carcinomas are a diverse group of tumours. Since 2014, the World Health Organization has classified adenosquamous carcinoma as a malignant epithelial tumour that combines invasive adenocarcinoma and squamous cell carcinoma [34, 35].

Glassy cell carcinoma of the uterine cervix is an extremely rare condition, contributing to approximately 1-2% of all cervical carcinomas as shown in Table **1** [36]. Glassy cell carcinoma (GCC) is characterized by cytoplasm with a finely granular or ground-glass appearance, distinct cell walls that stain with eosin and periodic acid-Schiff, and large nuclei with prominent nucleoli. The median age of patients diagnosed with cervical GCC is 46 years, with an age range of 33 to 69 years. The most common clinical symptoms include abnormal vaginal bleeding and postcoital bleeding [36, 37]. A militant histological variety of cervical cancer, neuroendocrine carcinoma of the cervix accounts for about 1-1.5% of all cervical malignancies [38]. These are of a rare type and are disunited into neuroendocrine tumours and neuroendocrine carcinoma. The clinical implications of NETs and NECs are comparable to those of other cervical malignancies, such as vaginal bleeding, discharge, and cervical masses, but their prognoses can vary [39].

Table 1. Cervical cancer types with percentages representing the total contribution to all carcinomas.

Sr. No.	Type of Carcinoma	Percent (%)
1	Squamous cell carcinoma	90-95
2	Adenocarcinoma	20-30
3	Adenosquamous carcinoma	5-10
4	Glassy cell carcinoma	1-2
5	Neuroendocrine carcinoma	1-1.5

4. PATHOGENESIS

The cervix uteri, the lower part of the uterus, consists of two sections: the endocervix (inner portion) and the ectocervix (outer portion). These areas meet at the transformation zone, which is particularly susceptible to pre-cancerous lesions caused by HPV. In this zone, the thin, flat squamous cells of the ectocervix come into contact with the columnar glandular cells of the endocervix. In 90% of cases, low-grade squamous intraepithelial lesions (LSIL), also known as cervical intraepithelial neoplasia stage 1 (CIN1), clear up on their own without treatment [40]. In most circumstances, re-infection can happen more than once without resulting in the development of cancer. Genetic diversity may be essential in resolving infection and limiting progression to invasive disease since only a tiny percentage of women who have HPV infection go on to acquire invasive cervical cancer [41]. Cervical intraepithelial neoplasia stages 2 and 3 (CIN2 and CIN3) and high-grade squamous intraepithelial lesions (H-SIL) are linked to a persistent HPV infection over time, progressive worsening of the lesions, viral load, tissue composition at the site of viral integration, and multiple reinfections (CIS) [42]. Together, these phases are referred to as high-grade dysplasia, and they have the potential to develop into invasive cervical cancer or carcinoma.

HPV16, the most common anogenital HPV type, is also the most dangerous. The pathogenicity of the different lineages of HPV16, HPV33, or HPV45 appears to be modulated by variations within the viral genome [43-45]. While the exact mechanisms causing the varying pathogenicity of distinct lineages are not fully understood, they could have to do with either variant splicing of viral oncogenes or differential expression levels [40]. Around 12% of squamous cell carcinoma and 37% of cervical adenocarcinomas globally are caused by HPV18, the second most carcinogenic HPV strain [41]. In invasive carcinoma or cervical intraepithelial neoplasia grade 3 (CIN3), HPV18 appears to fully integrate, while HPV16 can either fully integrate or persist as episomes [46]. Possible mechanisms include differences in promoter methylation, which have also been reported in HPV positive versus negative lesions, direct disruption of genes, or activation of retroelements [47-50]. The early genes E6 and E7, among others, are expressed when the viral DNA replicates inside the host cell. The well-characterized tumour suppressor p53 is known to bind to and be degraded by the E6 protein. This prevents apoptosis and builds up DNA damage inside the cells, which can cause unchecked cell division. The retinoblastoma (R-b) protein, which would normally sequester the transcription factor E2F, is bound by the E7 protein and rendered inactive. Moreover, cyclin-dependent kinase inhibitor 1A (p21 or CDKN1A), a tumour suppressor protein, and the p53 effector are muted by E7 [51, 52]. E2F causes uncontrolled cell growth by lifting the cell cycle checkpoint inhibition following Rb inactivation. Cyclin-dependent kinase inhibitor 2A (p16INK4A, or CDKN2A) expression is upregulated by E7 *via* E2F and serves as a predictive biomarker for cervical cancer. After that, CDKN2A becomes hypermethylated; nevertheless, since Rb is inhibited and p53 is damaged, CDKN2A inhibition is ineffective in stopping the cell cycle [53, 54].

Furthermore, this interferon-mediated response is rendered ineffective as soon as the HPV integrates within the cells. Although cytokines are expressed by keratinocytes and are essential for the activation of T-cells, macrophages, and Langerhans cells, it has been demonstrated that HPV episomes downregulate IL-1ß and IL-6 [55]. Mutagenesis can occur in the host cell as a result of HPV-induced p53 inactivation, unplanned replication, and uncontrollably growing cells. As in the case of all malignancies, the accumulation of somatic mutations and epigenetic modifications confers a selection advantage to the host genome [56]. Large-scale sequencing initiatives like the BioRAIDs and The Cancer Genome Atlas (TCGA) consortia have recently identified important genes and pathways for cervical cancer [46, 57]. Although it hasn't been well studied, some of them probably have differential regulation that affects the genetic predisposition to cervical cancer risk.

5. BIOMARKERS

Biomarkers are measurable biological indicators that play a crucial role in the management of cervical cancer, particularly in the context of surgical advancements, immunotherapy, targeted and conventional therapies, biopsy, colposcopy, and Pap smear integration. In surgical advancements, biomarkers help guide decisions about the extent of resection, tumour margins, and lymph node involvement, improving patient outcomes by tailoring surgical interventions to the individual's disease characteristics. In immunotherapy, biomarkers, such as PD-L1 expression, help identify patients most likely to benefit from immune checkpoint inhibitors, which enhance the body's ability to recognize and attack cancer cells. Similarly, in targeted therapies, specific biomarkers, such as HPV DNA and PIK3CA mutations, allow for the personalization of treatment by targeting molecular pathways that drive cervical cancer growth, leading to more precise inter-

ventions with fewer side effects than conventional chemotherapy. In conventional therapies like chemotherapy and radiation, biomarkers provide prognostic information and predict response to treatment, enabling oncologists to optimize therapeutic regimens and minimize unnecessary toxicity. Biopsies serve as the primary method for obtaining tissue samples to test for these biomarkers, allowing for molecular and histological analysis to determine tumour type, grade, and biomarker expression, which informs subsequent treatment plans. Colposcopy, often used following abnormal Pap smear results, allows for the visualization of the cervix and targeted biopsy collection, aiding in the detection of precancerous lesions and the identification of high-risk HPV strains. The Pap smear itself, while primarily a screening tool for early detection of cervical abnormalities, integrates biomarker analysis through the detection of HPV infection, a key etiological factor in cervical cancer development, thereby guiding further diagnostic and therapeutic measures. Together, the integration of biomarker testing across these diagnostic and therapeutic modalities facilitates a more personalized and effective management approach to cervical cancer, improving early detection, treatment response, and overall patient survival.

5.1. Biomarkers: For Detection of Cervical Cancer

The expression of the host's cervical cell cycle regulating proteins is altered by HPV infection. Such host proteins and nucleic acids with variable expression could serve as a "biomarker" for dysplastic cells. Examining such biomarkers could also lead to the discovery of novel pathways in the pathophysiology of cervical dyskaryosis caused by HPV.

5.1.1. P16 Biomarker

Tumour suppressor gene INK 4a encodes P16, which is a member of the class of cyclin-dependent kinase Cdk4/6 inhibitors. An essential function of the gene INK4a is to regulate the Cdk-Rb-E2F pathway [58]. In order to screen for cases of low-grade squamous intraepithelial lesion (LSIL), atypical squamous cells of unknown significance (ASC-US), and pap smear negative results, the p16 protein can be utilized as an additional supplement [59]. In HPV-induced cervical lesions, pRb is inactivated through interaction with the viral oncoprotein E7. Consequently, the Cdk-Rb-E2F regulatory pathway is thrown off balance, allowing inactivated pRb to effortlessly cross the G1/S cell cycle checkpoint. There is an overexpression of p16 in the reaction. In turn, the p16INK4a protein can be a marker of premalignant and malignant cervical epithelial cells [60].

5.1.2. Ki-67

The protein Ki-67, which is expressed during the G1, S, G2, and M phases of the cell cycle shown in Tables **2** and **3** and is found in the nuclei of developing cells, is linked to cell division. Ki-67 antigen can react with its monoclonal antibodyMIB-1 and therefore Ki-67/MIB-1 is known as a predictive factor for tumour development and its expression shows a correlation with poor prognosis in several types of cancer [61].

According to some research, both low and high grades of intraepithelial lesions exhibit increased proliferation as evidenced by Ki-67 immunohistochemical positivity. In others, the analysis's findings support the notion that Ki-67 and p16 have a significant correlation when it comes to identifying pre-invasive cervical lesions linked to HPV [58].

5.1.3. E Cadherin

E Cadherin is one of the essential adhesion molecules that determines the keratinocytes' development and architecture in that epithelium. Changes in these molecules' expression have been reported in intra-epithelial cervical carcinoma [62]. Adverse cervical lesions were linked to the reduction of E-cadherin protein. It may be possible to distinguish between precancerous and cancerous lesions more easily by using e--cadherin as a diagnostic biomarker [63]. The down-regulation is assumed to decrease cells' ability to adhere to one another and to aid in the shutdown of original tumors and metastases. As a result, the drop in E-cadherin expression appears to be a helpful indicator of cervical cancer's propensity to become malignant.

5.1.4. E6/ E7

E6 and E7 are RNA-based biomarkers, for identifying mRNA transcripts in cervical swabs to identify cervical precancerous lesions. Significant increases in HPV E6 and E7 mRNA and protein expression identify HPV infections that progress from transitory to transformative [64].

6. MARKETED FORMULATIONS

6.1. Diagnosis

Every woman was screened for cervical cancer using a Pap smear. The smear was collected with an Ayre spatula, spread on a glass slide, and then preserved in 95% ethyl alcohol for cytopathological analysis. All data was recorded using a pre-designed pro forma. The Pap smear is a simple, non-invasive, affordable, and effective method for detecting precancerous

Table 2. Biomarkers for cervical cancer.

Sr. No.	Biomarker	Type of Biomarker	Cell Cycle Phase	Role
1.	P16	Diagnostic marker	G1	This protein can be used as a biomarker that can add significant diagnostic precision in the assessment of Cervical Intra-epithelial Neoplasia lesions.
2.	Ki67	Prognostic marker	G1, S, G2, M	This protein has a function of growth in human tumours, and expression of its marker could suggest the degree of malignancy.
3.	E cadherin	Diagnostic marker	G1	A reduction in E-cadherin expression is a strong predictor of aggressive clinical behaviour and may indicate the need for adjuvant therapy in the early stages of cervical cancer patients. It also has a substantial impact on overall survival and disease-free survival.
4.	E6/ E7	Prognostic marker	G1, S	To detect mRNA transcripts in cervical swabs to detect precancerous lesions in the cervical region.

Table 3. Marketed formulation available used in the treatment of cervical cancer.

Brand Name	Active Drug	Dosage Form	Side Effect	References
Alymsys	Bevacizumab	Injection	Hives, difficulty breathing, lightheadedness, wheezing, coughing up blood	[65]
Avastin	Bevacizumab	Injection	Rectal bleeding, nosebleeds, protein in urine, inflammation of the nose	[66]
Bleomycin sulfate injection	Bleomycin	Injection	Stomatitis, interstitial pneumonia, hair loss, loss of appetite	[67]
Hycamtin	Topotecan Hydrochloride	Tablet	Tiredness, nausea, weakness, abdominal pain, indigestion	-
Keytruda	Pembrolizumab	Injection	Musculoskeletal pain, rash, fatigue, stomach pain	[68]
Tivdak	Tisotumab Vedotin - tftv	Injection	Hb level decreased, lymphocytes decreased, alopecia, epistaxis	[69]

lesions in gynaecological patients [70]. Colposcopy is a key diagnostic tool for women's health care, the colposcopy is especially important for the early diagnosis and prevention of cervical cancer. In this operation, the cervix, vagina, and vulva are closely examined using a specialized tool called a colposcope [71]. Using a speculum, a medical professional gently opens the vagina to inspect the cervix during a colposcopy. To help draw attention to any anomalies, the cervix is treated with an acetic acid solution says Valls J *et al.* [72] Colposcopy gives medical practitioners an enlarged view of these regions, making it possible to detect and assess problems that might not be apparent to the unaided eye. A colposcopy should be performed on women who have abnormal Pap tests, and a biopsy should be recommended for those who have abnormal colposcopy results says Sachan PL *et al.* [70] Biopsy is a process when a pathologist removes a sample of tissue from the cervix to examine under a microscope for indications of malignancy. Cervical cancer is detected by the following kinds of biopsies.

In the treatment of pre-invasive cervical cancer, a punch biopsy is a common office procedure usually performed alongside a colposcopy. It has an 88.8% positive predictive value for diagnosing cervical cancer. However, insufficient sampling can occur due to poor tissue preparation and transportation, non-representative biopsies, persistent bleeding, or severe tissue necrosis. In low-resource settings, gynaecological oncologists must consider the use of punch biopsies, clinical staging, and radiological assessments, especially for women who cannot afford or have renal complications (obstructive uropathy) that prevent examination under anaesthesia (EUA) [73]. When a patient has high-grade cytology, has received treatment for known or suspected cervical precancer in the past, is contemplating the observation of cervical intraepithelial neoplasia grade 2, or when the squamocolumnar junction is not entirely visible during a colposcopy, endocervical curettage is advised [74]. EC is a process that uses a curette, a spoon-shaped tool, to remove tissue or cells from the cervical canal. For any patient over 40, endocervical curettage is the recommended procedure. For all non-pregnant patients undergoing colposcopy, endocervical curettage is acceptable; however, it may be skipped in cases where an excisional procedure is planned later when the endocervical canal is not wide enough to accommodate a sampling device, or in nulli-

parous patients under the age of thirty. In these cases, the cytology report may indicate low-grade squamous intraepithelial lesions or atypical squamous cells of unknown significance, regardless of whether the squamocolumnar junction is fully visualized [75]. One common excisional technique for the diagnosis and management of CIN3 is the loop electrosurgical excision procedure, or - Loop Electrosurgical Excision Procedure (LEEP). However, up to 10% of patients have been documented to experience problems such as bleeding, infection, and perforation. The lesion may expand from the cervix's surface into the cervical canal, so it is crucial to remove enough of the cervix's transformation zone during the - LEEP in addition to excising the lesion [76]. A gynaecologic oncologist administered general anaesthesia during an in-patient LEEP with CC procedure. Using a 3.8-MHz radiosurgery equipment, -LEEP created a right-angled, triangular loop in a single pass. After the excision, a cold coagulator (120 °C) was administered to the cone bed for 10 to 20 seconds to stop the bleeding and destroy any remaining lesions. To identify cervical lesions, 5% acetic acid was applied to the cervix for one to two minutes before the surgery. After - Loop Electrosurgical Excision Procedure (LEEP, haemostatic treatments (such as fibrin sealant or Monsel's solution) were not used [77].

Cervical conization is a diagnostic procedure used to assess the tumour's characteristics and determine the extent of surgical treatment, helping to rule out invasion. It is also used to remove precancerous lesions or early-stage cancer. Conization is typically recommended when there is uncertainty about the most appropriate treatment approach [78]. The larger, cone-shaped tissue fragment that was removed from the cervix and cervical canal is being surgically removed [79]. It has become a crucial technique for minimally invasive surgery since it lowers the possibility of the tumour and abdominal cavity coming into touch during the procedure [80].

7. TESTS USED FOR CERVICAL CANCER STAGING INCLUDE

Clinical staging is used to assess key prognostic factors such as tumour size, parametrial invasion, endocervical extension, pelvic side wall or adjacent/distal organ involvement, and lymph node status. Cross-sectional imaging modalities such as computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography-CT (PET-CT) are increasingly used in the study of cervical cancer. In addition, monitoring cervical cancer, assessing how well a tumour responds to therapy, and choosing the right patients for less invasive procedures such as radical trachelectomy to preserve fertility are also considered imaging indications. While CT is similarly useful for assessing the extrauterine spread of the illness, MRI is the recommended imaging modality for evaluating local cervical cancer. When it comes to identifying metastasized lymph nodes and tumour recurrence, PET-CT performs quite well diagnostically says Bourgioti C *et al.* [81] In a Visual examination of the cervix, the cervix is exposed to 5% acetic acid during this test. The aberrant areas with enhanced nuclear material and protein are dehydrated by acetic acid. While the normal cells that carry glycogen stay normal, the aberrant portions become acetowhite. Another option is to use Schiller's iodine (VILI, or visual inspection with Lugol's iodine). Glycogen-containing healthy cells in VILI absorb iodine and turn mahogany brown, while aberrant regions do not. A biopsy can then be performed on these suspicious spots. Sharp white plaques with thick margins are classified as HSIL (high-grade squamous intraepithelial lesion), while dull white plaques with fuzzy borders are classified as LSIL (low-grade squamous intraepithelial lesion). Even with its limited specificity, it has a very low false-negative rate. Therefore, in an environment with limited resources where pap screening is not available, *via* may prove to be a useful substitute [82].

7.1. Treatments

Surgery to remove the cervix is called a trachelectomy. The cervix, vaginal margins, and parametria are removed all at once during a radical trachelectomy, leaving the uterine body and fundus in place. Radical trachelectomy for fertility-preserving treatment of cervical cancer is widely reported in the literature as shown in Fig. (**3**) [83]. A hysterectomy, which involves the removal of the cervix and uterus, is a common treatment for early-stage cervical cancer. The standard treatment for early-stage cases (IA2 to IIA) is a radical hysterectomy combined with pelvic lymphadenectomy. This surgery can be performed either through laparotomy (open surgery) or laparoscopy (minimally invasive surgery using conventional or robotic techniques). During a radical hysterectomy, the womb, fallopian tubes, upper part of the vagina, and tissues surrounding the cervix are removed, and sometimes the ovaries are also resected. Retrospective studies, including those by Ramirez PT *et al.*, show that laparoscopic radical hysterectomy is associated with less blood loss during surgery, a shorter hospital stay, and fewer postoperative complications compared to open abdominal surgery in early-stage cervical cancer patients [84].

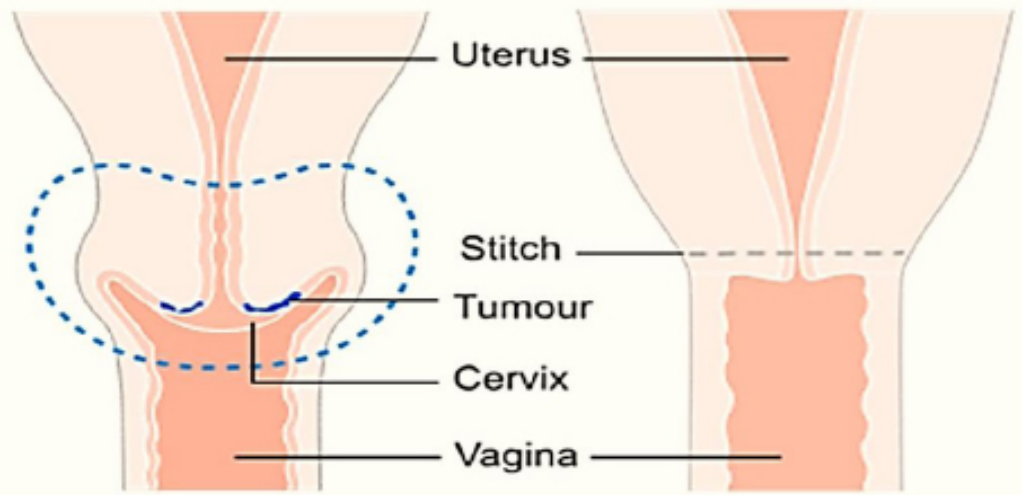

Fig. (3). Excision of the cervix, upper vagina, and lymph nodes during a radical trachelectomy for cervical cancer. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

One of the most popular forms of treatment for cervical cancer is radiotherapy using high-energy x-rays, which includes brachytherapy and external beam radiation. With the use of SEER*Stat software (Surveillance, Epidemiology, and End Results [SEER] Programme), cervical cancer cases were obtained from the SEER database. Differential proportional hazards age, TNM stage, tumor size, first surgery, and various radiation modalities were all assessed for their prognostic significance using the Cox model. According to the study, radiation therapy is beneficial in patients who did not undergo primary surgery, diagnosed at an older age (≥45 years old), at advanced TNM stages (III/IV), or with larger tumour size (≥3 cm) [85].

Chemotherapy is an essential component of the standard treatment plan for cervical cancer and is usually given in addition to radiotherapy as an adjuvant therapy after surgery when poor prognostic tumor features raise the likelihood of recurring illness says Chao Ji *et al.* The recommended course of treatment for cervical cancer in stage IVB is chemoradiotherapy. Cancer patients' body composition indicators, such as visceral obesity, have been the subject of much research about their prognostic consequences. Patients with stage IVB cervical carcinoma have an improved prognosis if they are viscerally obese before chemoradiation therapy. Patients with stage IVB cervical carcinoma have an improved prognosis if they are viscerally obese before chemoradiation therapy [86].

Chemotherapy with immunotherapy: A tumor microenvironment that is immunosuppressive in situ is present in treatment-naive cervical cancer. Both regulatory T cells and indoleamine 2,3-dioxygenase positive (IDO^+) cells can be effectively reduced by neoadjuvant chemotherapy (NACT). NACT is known to improve antigen presentation in responders and facilitate the infiltration of effector T cells. NACT based on platinum can dramatically lower Tregs and improve responders' antigen presentation, which in turn encourages the invasion of $CD8^+$ and $CD4^+$ T cells. According to Xue Feng *et.al.*, this gives a theoretical foundation for the timing of immunotherapy; that is, patients may benefit more from immunotherapy administered after chemotherapy [87].

Chemotherapy with ^{125}I brachytherapy was suggested by Zhimei Huang *et al,* patients receiving chemotherapy alone versus those receiving chemotherapy and ^{125}I brachytherapy together underwent a comparative analysis. Kaplan-Meier curves, log-rank tests, Cox proportional hazard regression, and propensity score matching (PSM) (1:1) were used to evaluate overall survival (OS) and progression-free survival (PFS). The study suggested that the combination of ^{125}I brachytherapy and chemotherapy results in better therapeutic outcomes [88].

7.2. Chimeric Antigen Receptor T-cell (CAR-T)

Chimeric Antigen Receptor T-cell (CAR-T) therapy is a breakthrough technique within the area of immunotherapy, bringing renewed hope to patients with cervical cancer. This revolutionary cellular therapy involves the genetic alteration of a patient's T cells to express a CAR that selectively targets tumour-associated antigens. Once modified, these T cells are reinfused into the patient, where they can recognize and destroy

cancer cells more efficiently. The method begins with the isolation of T cells from the patient's blood. These cells are then changed in the laboratory to integrate a CAR, which is designed to bind to specific proteins produced on the surface of cervical cancer cells, such as E6 and E7 proteins generated from human papillomavirus (HPV). This focused method boosts the T cells' ability to locate and eradicate cancer cells while protecting healthy tissues, lowering potential adverse effects compared to standard medicines. Recent trials have demonstrated promising results for CAR-T therapy in cervical cancer, particularly in instances that are recurring or resistant to traditional treatments. For instance, clinical trials have revealed that CAR-T cells can lead to considerable tumour regression in patients, showing its promise as a viable therapy option. Moreover, improvements in CAR-T technology, including the production of dual-targeted CAR-T cells and the insertion of safety switches, aim to improve efficacy and decrease unwanted effects. Researchers are now researching combinations of CAR-T therapy with other treatment modalities, such as immune checkpoint inhibitors, to further optimize therapeutic effects. CAR-T therapy stands out as a promising frontier in cervical cancer immunotherapy, displaying its ability to harness the power of the immune system in a tailored manner. As research improves, it holds the potential to alter therapy paradigms and improve the prognosis for people battling this tough malignancy.

7.3. Targeted Therapy

Targeted treatments are made particularly to block substances, usually proteins, that are expressed only by cancer cells and that are in charge of limiting the development, multiplication, and dissemination of cancer [89]. Targeted therapies are designed to be more selective for cancer cells than normal cells, making them potentially more effective and less likely to cause side effects compared to current chemotherapies. As researchers gain a deeper understanding of the molecular mechanisms behind cervical cancer, they have identified oncogenic pathways that can be targeted for treatment. This has been especially important for patients with poor prognoses due to metastatic or recurrent cervical cancer, offering new hope for more effective interventions [89]. An FDA-approved frontline nano-formulation for the treatment of advanced metastatic tumours is paclitaxel (PTX) encapsulated in albumin. Conversely, difluorinated curcumin is a powerful and new synthetic curcumin analog that is being tested for many cancers. PTX and difluorinated curcumin were encapsulated in folic acid-decorated bovine serum albumin nanoparticles, namely FA-BSA-PTX and FA-BSA-CDF, respectively to increase the bioavailability and targeting ability. Both formulations produced homogenous nano-sized particles with smooth surface morphology, negative surface potential, and high drug-loading efficiency. Combination regimens are becoming conventional weapons in the fight against several lethal malignancies due to the heterogeneity and complexity of various cancers. According to Gawde *et. al*., the study shows that the synergistic anticancer effect provided by FA-BSA-CDF and FA-BSA-PTX was enhanced *via* folate receptor-mediated targeted uptake and apoptosis induction [90]. According to Mahalingam Mahalakshmi *et al,* phloroglucinol, a bioactive natural chemical, is conjugated with gold nanoparticles to target the mitochondrial transmembrane potential of HeLa cancer cells. Their sharp features enhance surface plasmon resonance, shape, surface charge, and stability. The results showed that combining gold with nanoparticles scavenges free radicals and induces cell death in HeLa cancer cells. Additionally, fluorescence microscopy studies demonstrated that gold-nano conjugates trigger apoptosis by promoting the penetration of the mitochondrial membrane [91]. The combined chemo-photothermal properties of nanocomposites may make them more potent tumor-fighting agents, according to Jia *et al.* Gemcitabine (GEM) for targeted cancer therapy was delivered using polydopamine (PDA)-loaded with polyethylene glycol and folic acid (FA). When FA modification boosted intracellular absorption of nanoparticles, HeLa cells' capacity to recover was significantly diminished, and cancer cells underwent apoptosis [92].

Orlistat's (ORL) formulation and clinical application are limited by its low oral bioavailability and poor water solubility Figs. (**4** and **5**). To improve the intrinsic solubility and therapeutic effects of Orlistat, additional strategies must be considered. In a study by Nascimento *et al.*, Orlistat was encapsulated in polymeric aqueous nanocapsules to evaluate its *in vitro* cytotoxic activity in HeLa cervical cancer cells. Poly(ε-caprolactone) was used to prepare the nanocapsules containing Orlistat (NC-ORL) through the interfacial deposition of a preformed polymer. Nanoencapsulation significantly enhanced Orlistat's cytotoxic effect compared to its non-encapsulated form. This novel nanoformulation presents a promising alternative to current treatments for cervical cancer, a major global health issue for women, by improving Orlistat's solubility and enabling the development of localized drug delivery systems [93]. The process of a tumour growing, encroaching, and metastasizing depends critically on angiogenesis and the angiogenic agents produced. As they carry nutrients and oxygen while eliminating catabolites,

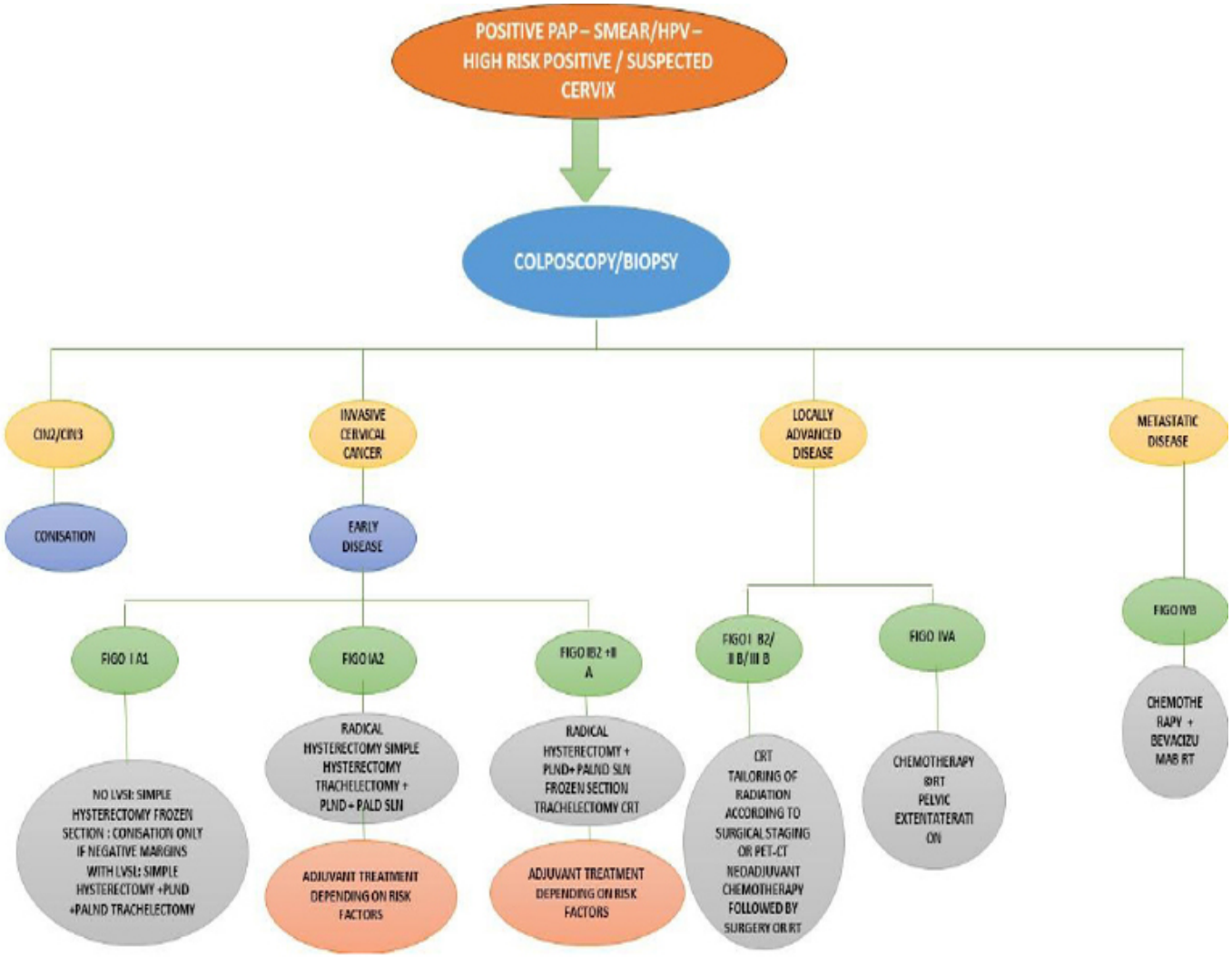

Fig. (4). An overview of cervical cancer management and care. Treatment written in green refers to radiotherapy, grey refers to surgical and orange refers to chemotherapy. Sentinel lymph node biopsy (SLN), pelvic lymph node dissection (PLND), chemo-radiotherapy (CRT), and radiotherapy (RT)*. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

new vessels encourage growth. The so-called "angiogenic switch" is essentially a growth mechanism that all tumours undergo when they move from an avascular to a vascular phase shown in Fig. (**6**). An overexpression of a positive regulator of angiogenesis is caused by an oncogene in certain tumours. It has been demonstrated that inhibiting proangiogenic factors is a successful method of limiting the growth of CC tumours [94]. Sunitinib malate is an oral medication that inhibits angiogenesis and cell division by targeting multiple receptors, including FLT3, c-KIT (stem cell factor receptor), PDGFR-α, PDGFR-β, VEGF-2, and VEGF-3. It is approved for treating renal cancer and gastrointestinal stromal tumours resistant to imatinib. However, in a Phase II trial, sunitinib did not show any objective responses in pretreated patients with locally advanced or metastatic cervical cancer (CC). Additionally, a higher rate of fistula formation (26%) was observed compared to other biologics studied in similar Phase II trials [95]. A multitargeted receptor TKI of VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-α, PDGFR-β, and c-kit, pazopanib is taken orally. Approved for the treatment of kidney cancer, it inhibits angiogenesis and prevents tumour growth.104% of Patients with previously treated advanced cancer of the kidney were enrolled in randomized Phase II research to compare pazopanib, lapatinib, or both. Based on the extended PFS and advantageous toxicity profile, this research proved

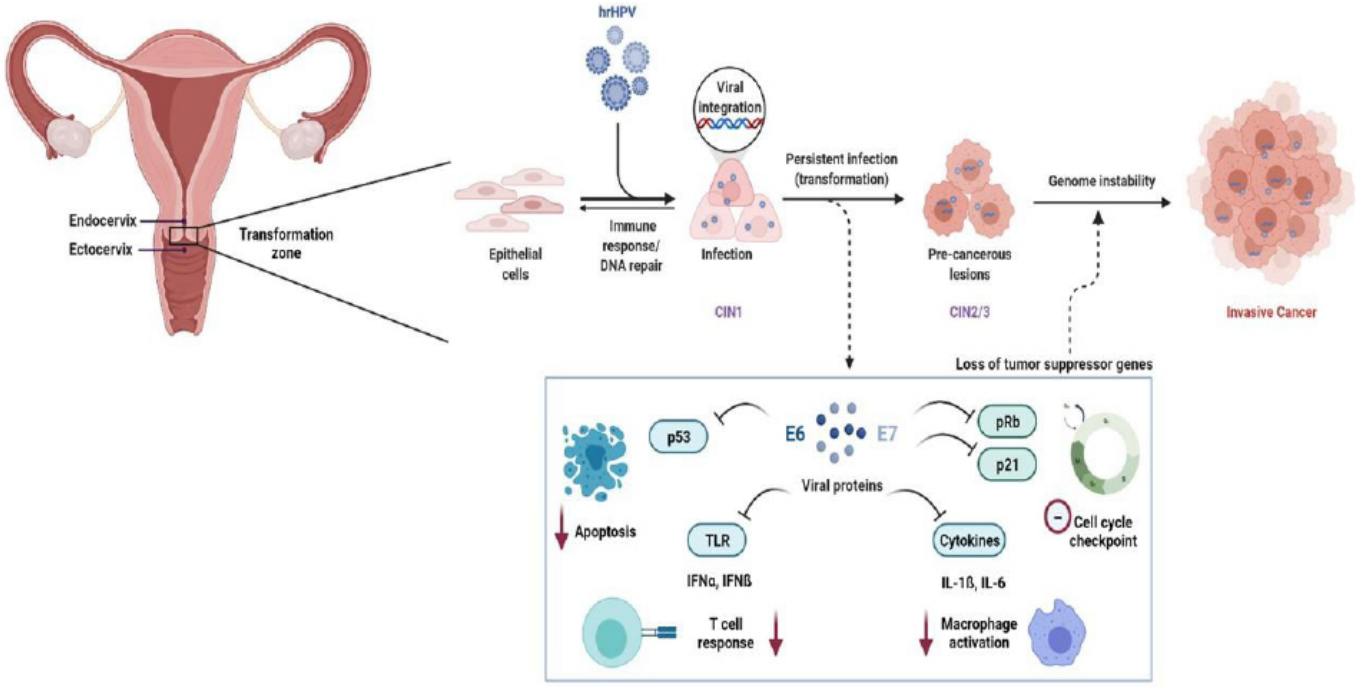

Fig. (5). Pathogenesis of cervical cancer. Following a prolonged infection with high-risk HPV (hrHPV), epithelial cells in the cervix's transformation zone develop lesions. Some patients have resolution of the lesions, while in others, cells transform viral integration and advance from I to II and III cervical intraepithelial neoplasia (CIN1, CIN2, and CIN3). After release, the viral proteins E6 and E7 block the actions of TP53-mediated apoptosis, p21-mediated cell cycle checkpoints, toll-like receptors (TLRs)-mediated T-cell responses, and cytokines-mediated macrophage activation. Further CIS or invasive cervical cancer (C-C) as well as unchecked cell proliferation and genomic instability result from this, as does an inadequate immune response and viral replication. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

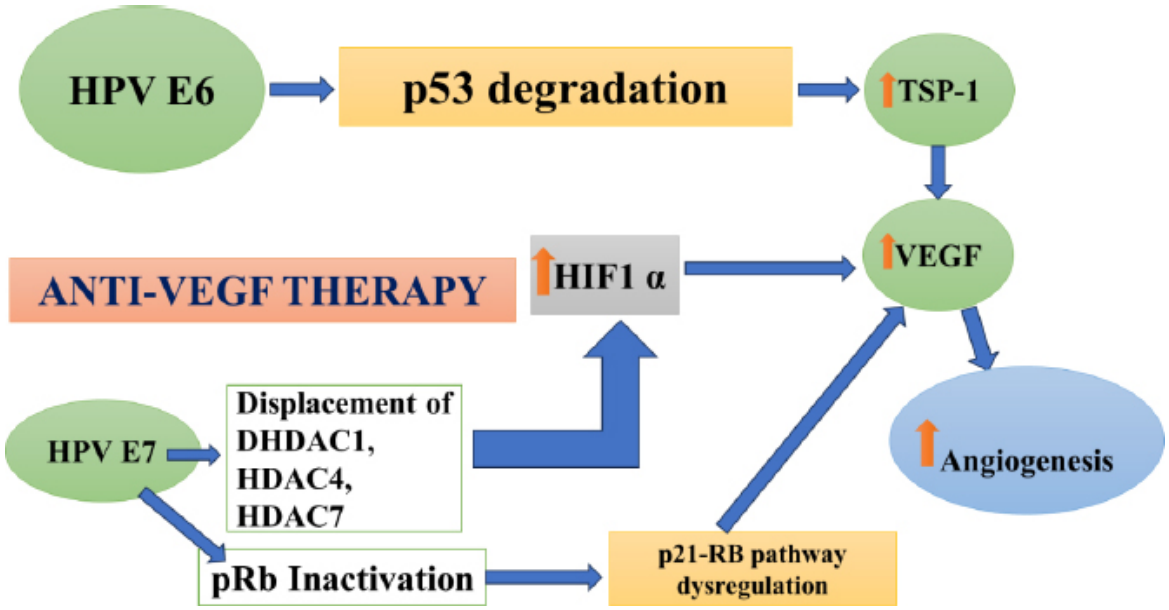

Fig. (6). The use of anti-angiogenic therapy in the treatment of cervical cancer is justified by biology. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

the efficacy of pazopanib. Diarrhea, nausea, hypertension, and anorexia were the most frequently reported toxicities associated with pazopanib [96]. Brivanib alaninate is a tiny chemical that can be taken orally and selectively inhibits the fibroblast growth factor receptor (FGFR) and VEFGR. Brivanib's principal target is the VEGFR because it is a first-generation FGFR inhibitor. Through VEGFR inhibition, it has antiangiogenic and anticancer properties. FGFR can act as a compensating signal for VEGFR and is also involved in basic FGF-mediated angiogenesis and tumour cell proliferation. Consequently, the first-generation inhibitor's inhibition of FGFR may lessen FGFR's ability to compensate for VEGFR, leading to stronger antitumor effects [97]. C-kit, PDGFR, and tyrosine kinase are specifically inhibited by imatinib, a 2-phenylaminopyrimidine derivative. Malignant gastrointestinal stromal tumours and chronic myeloid leukaemia patients have shown it to have outstanding clinical efficacy [98]. A pilot trial by Candelaria *et al.* assessed imatinib mesylate as a potential second-line treatment for PDGFR-α--expressing cancer that recurs or spreads [99, 100].

7.4. Immunotherapy

A novel cervical cancer treatment called immunotherapy that targets HPV oncoproteins has received a lot of attention and appears to have a lot of potential. This treatment has the benefit of selectively targeting malignant and dysplastic precancerous cervical epithelial cells that express HPV oncoproteins [101, 102]. This strategy has gained popularity and produced several laboratory and clinical advancements, such as the creation of vaccines, inhibitors or checkpoint blockers, and adoptive T cell treatment for cervical cancer. Many of these immunotherapies are in clinical trials and have variable success rates [101, 103].

A clinical experiment including a therapeutic HPV-16 specific vaccination shown its ability to target preinvasive dysplastic lesions, leading to a 79% response rate in cases with HPV-positive grade 3 vulvar intraepithelial neoplasia says Kenter GG *et al.* [104] Additional vaccinations that target the oncoproteins E6 and E7 of HPV-16 and -18 can be peptide- and protein-based, or live-vector based, utilizing bacterial and viral vectors, and are summarized in Table **4** [105]. PD-1, its ligands PD-L1 and PD-L2, and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) are immune-suppressive brakes that are released when immune-suppressive mediators such as ICIs are activated [101, 106]. It has been proposed that PD-L1, which is expressed on the surface of TILs and antigen-presenting cells, contributes to the onset and duration of HPV infections by suppressing T cell function. Even when it is close to CIN or cancer cells, it is uncommon to find it in normal cervical tissue. Owing to the strong correlation between HPV infection and cervical cancer, blocking PD-1 or its ligands can potentially disrupt the inhibitory PD-1/PD-L1 relationship and reinstate T cell--mediated death [107-109]. FDA-approved ICIs that target PD-1/PD-L1 include nivolumab, which is used to treat metastatic and recurrent cervical cancer, and pembrolizumab, which is useful in treating solid tumors from PD-L1 positive cervical cancer [110-112]. T cell activation is negatively regulated by the checkpoint protein receptor CTLA-4, which suppresses the immune system by preventing T cells from responding to cancer cells and demonstrating antitumor immunity [113, 114]. Unsurprisingly, it has been demonstrated that CTLA-4 inhibition helps the body overcome the immunological suppression linked to HPV-driven malignancies. It is true that ipilimumab, a humanized monoclonal antibody that targets CTLA-4, significantly activated the immune system in peripheral blood, although not significantly increase the tumour response in patients with cervical cancer [115]. In recurrent or metastatic cervical cancer, the combination of PD-1 and CTLA-4 receptor inhibitors, such as nivolumab and ipilimumab, has demonstrated long-lasting therapeutic effectiveness, independent of PD-L1 status. The side effects associated with this combination were under control and consistent with earlier reports of combination therapy including nivolumab and ipilimumab [116]. Nevertheless, ipilimumab treatment following chemotherapy and radiation therapy alone improved the anti-tumour response to cervical cancer, indicating that this possible combination may give patients at high risk of disease recurrence a desired immune system boost [117].

Although the phase II experiment is still underway and further studies must be conducted, LN-145 TIL, an ACT, has demonstrated an 89% disease control rate and a 44% objective response rate [103]. The potential of using LN-145 TIL followed by interleukin-2 (IL-2) for the treatment of patients with recurrent, metastatic cervical carcinoma who have undergone non-myeloablative lymphodepletion is being investigated in an early phase I study, which is based on the tentative trial results [118]. Before immunotherapy, lymphodepletion is a technique used to reduce lymphocyte and T cell activity since host immunosuppressive T cells may impede the total removal of cancers that have already progressed [119]. According to Wrzesinski C *et al,* gaining more exposure to activating cytokines, recognizing low-affinity antigens more readily, and being less vulnerable to regulatory elements' repression are some benefits of lymphodepletion [120].

Table 4. Immunotherapies for cervical cancer.

Immunotherapy	Specific Target	Authors	Therapeutic Agent	CIN/Cervical Cancer Stage	Outcomes
Vaccines	HPV-16 E7 fusion protein	Basu P *et al.*	ADXS11-001 (bacterial) [123]	Advanced/persistent/ recurrent	Significant clinical activity with observed prolonged survival, tumour responses, and stabilization of recurrent disease compared to a current chemotherapeutic agent, cisplatin.
	HPV-16 E6 and E7 peptide	Borysiewicz LK *et al.* and Kaufmann AM *et al.*	TA-HPV (viral) [124, 125]	Progressive	Well tolerated with vaccination-inducing HPV-specific cytotoxic T lymphocytes in 13.8-37.5% of patients, and 27.6-37.5% of patients developed HPV-specific responses with likely therapeutic benefit.
		Roman LD *et al.*	SGN-00101 [126]	High-grade CIN	Induced lesion regression which correlated with immune response
	HPV-16 E7 HLA-A2 restricted peptide	Garcia F *et al.*	ZYC101a [127]	High-grade CIN	suggesting enhanced immunogenicity. Well-tolerated in all patients and promoted resolution of CIN 2/3 in women younger than 25 years.
	Plasmid targeting HPV-16/18 E6 and E7	Trimble CL *et al.*	VGX-3100 [128]	CIN2/3 associated with HPV-16/HPV-18	First therapeutic vaccine to show efficacy against CIN2/3 associated with HPV-16 and -18. Erythema is significantly more common in the
Immune checkpoint inhibitors (ICIs)	PD-1/PD-L1	Browne I *et al.* and Frenel JS *et al.*	Pembrolizumab [110, 111]	PD-L1 positive tumours	VGX-3100 group (78□4%) compared to the control group (57.1%). Exhibits effective antitumour activity and improved toxicity profile.
		Naumann RW *et al.*	Nivolumab [112]	Advanced/recurrent	Warrants further investigation as no new safety signals were identified in the patients investigated.
		Rischin D *et al.*	Cemiplimab [129]	Recurrent/metastatic	Demonstrated clinical benefit and a safety profile comparable to that observed with other PD-1 inhibitors for platinum and taxane doublet-resistant/intolerant patients.
		O'Malley DM *et al.*	Balstilimab [130]	Recurrent/metastatic	Resulted in meaningful and durable clinical activity and manageable
	CTLA4	Finja S *et al.*	Ipilimumab [4]	Metastatic/locally advanced/recurrent	safety. Did not elicit a significant patient tumour response.
		Da Silva DM *et al.*	*Following chemoradiation (CRT):* Ipilimumab [117]	Metastatic/locally advanced/recurrent	Expression of the PD-1 significantly increased on T-cell subsets following CRT and was sustained or increased following ipilimumab treatment. This treatment significantly expanded central and effector memory T-cell populations.
Adoptive T cell therapy (ACT)	Tumour-infiltrating lymphocytes (TILs)	Edwards RP *et al.*	LN-145 TIL [103]	Recurrent/persistent/ metastatic	Acceptable safety and efficacy profile, and results in 44% objective response rate and 89% disease control rate in patients previously treated for cervical cancer.
		Mauricio D *et al.*	LN-145 TIL + IL-2 [118]	Recurrent/persistent/ metastatic	No results yet.
		Langhan MM *et al.*	Young TIL [121]	Metastatic squamous cell carcinoma and adenocarcinoma	Objective tumour responses in 3/9 patients with durable complete regression. HPV reactivity of infused T cells correlated positively with clinical responses and remained significant even 1 month after treatment.

Since ACT is a highly customized treatment, it may avoid the use of chemotherapy and its associated drawbacks in cases of cervical cancer, although more research is needed [121]. In order to achieve higher response rates, there is a general shift towards using a combination approach to immunotherapies, either with other immunotherapies or with currently available medicines [122].

7.5. Clinical Trial Status for Cervical Cancer Therapy

Clinical trials play a crucial role in advancing cervical cancer treatment by evaluating the efficacy and safety of new therapeutic strategies. Table **5** summarizes various clinical trials, including Phase 1, 2, and 3 studies of drugs such as Celecoxib, Taxotere (Docetaxel), and Gemcitabine in combination with radiotherapy and chemotherapy, highlighting both completed and ongoing trials that continue to shape the landscape of cervical cancer therapy.

8. LIMITATIONS AND SIDE EFFECTS

Over the past decade, cervical cancer treatments have evolved significantly with new therapeutic modalities aimed at improving patient outcomes and minimizing side effects. Surgical advancements, such as minimally invasive procedures and robotic surgeries, have led to faster recoveries and less blood loss, though these techniques are limited to early-stage cancers. Chemotherapy, a staple in cervical cancer treatment, has seen the introduction of novel drug combinations that enhance tolerance and efficacy, but it remains non-specific, damaging healthy cells and sometimes leading to resistance. Radiation therapy has also progressed, particularly with brachytherapy, which targets cancer more precisely. Despite this, it carries risks like skin irritation and potential tissue damage. Immunotherapy, especially immune checkpoint inhibitors such as PD-1/PD-L1 inhibitors, offers promising results for advanced cases but can trigger autoimmune reactions and is costly. Moreover, these therapies only benefit select patient groups. Targeted therapies have been developed to attack molecular pathways like EGFR and VEGFR, offering more personalized approaches. However, their effectiveness is limited by resistance and the need for tumours to express these targets. Nanoparticle-based delivery systems, which enhance drug bioavailability and targeting precision, are emerging as a revolutionary approach with fewer systemic side effects, although they are still in the experimental phase and have unknown long-term effects (Table **6**).

Table 5. Clinical trial status of drugs for cervical cancer.

Sr. No.	Drug	CT No.	Condition	CT Phase	Current Status
1.	Celecoxib	NCT00152828	Cervix neoplasms	Phase 2	Completed
2.	Taxotere (Docetaxel) with concurrent radiotherapy	NCT00178269	Cervix neoplasm	Phase 2	Completed
3.	Nelfinavir+ Cisplatin chemotherapy+ pelvic radiation	NCT02363829	Uterine cervix cancer	Phase 1	Completed
4.	Cetuximab, cisplatin and radiotherapy	NCT02363829	Cancer of the cervix	Phase 2	Unknown status
5.	Radiotherapy + Metronidazole	NCT01937650	Cervix carcinoma	Phase 3	Completed
6.	Cisplatin + radiation + sorafenib	NCT00510250	Cancer of the cervix	Phase 2	Completed
7.	Gemcitabine, cisplatin and radiation vs cisplatin and radiation	NCT00191100	Cancer of the cervix	Phase 3	Completed

Table 6. Advancements in therapeutic modalities, side effects, and limitations.

Therapeutic Modality	Advancements	Side Effects	Limitations
Surgery	Minimally invasive techniques, robotic surgeries, fertility-sparing options	Lower blood loss, faster recovery	Not suitable for advanced stages of cancer
Chemotherapy	New drug combinations improving tolerance and efficacy	Nausea, hair loss, risk of infection	Non-specific, affecting healthy cells, potential for resistance
Radiation Therapy	Targeted radiation, brachytherapy	Skin irritation, fatigue, tissue damage	Risk of secondary cancers, limited use in metastatic cases
Immunotherapy	Immune checkpoint inhibitors (*e.g.*, PD-1/PD-L1 inhibitors)	Autoimmune reactions, fatigue	High cost, works for select patient groups
Targeted Therapy	Focus on molecular targets like EGFR, VEGFR	Hypertension, proteinuria, fatigue	Resistance development, limited to tumours expressing targets
Nanoparticle-Based Delivery	Increased bioavailability and precision in drug targeting	Minimal systemic side effects compared to traditional methods	Still experimental, long-term effects unknown
Combination Therapies	Enhanced tumour control with reduced side effects	Dependent on patient-specific factors	Risk of cumulative toxicity, higher treatment cost

9. FUTURE TRENDS

There will likely be major developments in the diagnosis and treatment of cervical cancer in the future. Artificial intelligence and liquid biopsies are examples of emerging technology that could lead to less intrusive and more precise diagnostic procedures. Furthermore, it is anticipated that customized therapeutic modalities, such as immunotherapy and targeted medicines, will enhance results while reducing adverse effects. In the upcoming years, the care of cervical cancer may undergo a revolution if these technologies are incorporated into clinical practice.

CONCLUSION

In summary, although improvements in detection and therapy present a bright future, cervical cancer still poses a serious threat to public health. For the best possible patient outcomes, early detection *via* enhanced screening techniques and a multimodality treatment plan customized for each patient is essential. There is still room to reduce the incidence of cervical cancer by further investigating non-invasive diagnostics, personalized medicine, and innovative treatments like immunotherapy. For the provision of equitable healthcare, it is also imperative to address differences in access to screening and treatment.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Roy, P.S.; Saikia, B.J. Cancer and cure: A critical analysis. *Indian J. Cancer,* **2016**, *53*(3), 441-442. http://dx.doi.org/10.4103/0019-509X.200658 PMID: 28244479

[2] Torre, L.A.; Siegel, R.L.; Ward, E.M.; Jemal, A. Global cancer incidence and mortality rates and trends—an update. *Cancer Epidemiol. Biomarkers Prev.,* **2016**, *25*(1), 16-27. http://dx.doi.org/10.1158/1055-9965.EPI-15-0578 PMID: 26667886

[3] Malagón, T.; Louvanto, K.; Ramanakumar, A.V.; Koushik, A.; Coutlée, F.; Franco, E.L. Viral load of human papillomavirus types 16/18/31/33/45 as a predictor of cervical intraepithelial neoplasia and cancer by age. *Gynecol. Oncol.,* **2019**, *155*(2), 245-253. http://dx.doi.org/10.1016/j.ygyno.2019.09.010 PMID: 31604665

[4] Seifert, F.; Eisenblätter, R.; Beckmann, J.; Schürmann, P.; Hanel, P.; Jentschke, M.; Böhmer, G.; Strauß, H.G.; Hirchenhain, C.; Schmidmayr, M.; Müller, F.; Fasching, P.; Luyten, A.; Häfner, N.; Dürst, M.; Runnebaum, I.B.; Hillemanns, P.; Dörk, T.; Ramachandran, D. Association of two genomic variants with HPV type-specific risk of cervical cancer. *Tumour Virus Research,* **2023**, *16*, 200269. http://dx.doi.org/10.1016/j.tvr.2023.200269 PMID: 37499979

[5] Burmeister, C.A.; Khan, S.F.; Schäfer, G.; Mbatani, N.; Adams, T.; Moodley, J.; Prince, S. Cervical cancer therapies: Current challenges and future perspectives. *Tumour Virus Res.,* **2022**, *13*, 20023.

[6] Perkins, R.B.; Wentzensen, N.; Guido, R.S.; Schiffman, M. Cervical cancer screening. *JAMA,* **2023**, *330*(6), 547-558. http://dx.doi.org/10.1001/jama.2023.13174 PMID: 37552298

[7] Muhammad Husni, C.; Agus Priyo, W.; Upik Anderiani, M.; Berti, N.; Rina, M.; Syahrul, R.; Syarifuddin, W. Detection of human papilloma virus (HPV) in parafin block of cervical cancer patients using multiplex polymerase chain reaction (PCR) and reverse line blot methods. *Medicina Clínica Práctica,* **2021**, *4*, 100225.

[8] Li, X.; Zhang, Y.; Wu, H.; Li, S.; Ge, S.; Gao, J. A case of neoadjuvant chemotherapy in pregnancy with cervical cancer (IB3). *Cancer Treat. Res. Commun.,* **2024**, *38*, 100749. http://dx.doi.org/10.1016/j.ctarc.2023.100749 PMID: 38184968

[9] Plummer, M.; Peto, J.; Franceschi, S. Time since first sexual intercourse and the risk of cervical cancer. *Int. J. Cancer,* **2012**, *130*(11), 2638-2644. http://dx.doi.org/10.1002/ijc.26250 PMID: 21702036

[10] Zhang, S.; Xu, H.; Zhang, L.; Qiao, Y. Cervical cancer: Epidemiology, risk factors and screening. *Chin. J. Cancer Res.,* **2020**, *32*(6), 720-728. http://dx.doi.org/10.21147/j.issn.1000-9604.2020.06.05 PMID: 33446995

[11] Chen, Q.; Huang, Y.; Shao, L.; Han-Zhang, H.; Yang, F.; Wang, Y.; Liu, J.; Gan, J. An *EGFR*-amplified cervical squamous cell carcinoma patient with pulmonary metastasis benefits from afatinib: A case report. *OncoTargets Ther.,* **2020**, *13*, 1845-1849. http://dx.doi.org/10.2147/OTT.S236382 PMID: 32184619

[12] Tewari, K.S.; Sill, M.W.; Long, H.J., III; Penson, R.T.; Huang, H.; Ramondetta, L.M.; Landrum, L.M.; Oaknin, A.; Reid, T.J.; Leitao, M.M.; Michael, H.E.; Monk, B.J. Improved survival with bevacizumab in advanced cervical cancer. *N. Engl. J. Med.,* **2014**, *370*(8), 734-743. http://dx.doi.org/10.1056/NEJMoa1309748 PMID: 24552320

[13] Thibult, M.L.; Mamessier, E.; Gertner-Dardenne, J.; Pastor, S.; Just-Landi, S.; Xerri, L.; Chetaille, B.; Olive, D. PD-1 is a novel regulator of human B-cell activation. *Int. Immunol.,* **2013**, *25*(2), 129-137. http://dx.doi.org/10.1093/intimm/dxs098 PMID: 23087177

[14] Bhatla, N.; Berek, J.S.; Cuello Fredes, M.; Denny, L.A.; Grenman, S.; Karunaratne, K.; Kehoe, S.T.; Konishi, I.; Olawaiye, A.B.; Prat, J.; Sankaranarayanan, R.; Brierley, J.; Mutch, D.; Querleu, D.; Cibula, D.; Quinn, M.; Botha, H.; Sigurd, L.; Rice, L.; Ryu, H.S.; Ngan, H.; Mäenpää, J.;

Andrijono, A.; Purwoto, G.; Maheshwari, A.; Bafna, U.D.; Plante, M.; Natarajan, J. Revised FIGO staging for carcinoma of the cervix uteri. *Int. J. Gynaecol. Obstet.,* **2019**, *145*(1), 129-135. http://dx.doi.org/10.1002/ijgo.12749 PMID: 30656645

[15] Bhatla, N.; Aoki, D.; Sharma, D.N.; Sankaranarayanan, R. Cancer of the cervix uteri. *Int. J. Gynaecol. Obstet.,* **2018**, *143*(S2)(Suppl. 2), 22-36. http://dx.doi.org/10.1002/ijgo.12611 PMID: 30306584

[16] Nicolet, V.; Carignan, L.; Bourdon, F.; Prosmanne, O. MR imaging of cervical carcinoma: A practical staging approach. *Radiographics,* **2000**, *20*(6), 1539-1549. http://dx.doi.org/10.1148/radiographics.20.6.g00nv111539 PMID: 11112809

[17] Nanthamongkolkul, K.; Hanprasertpong, J. Predictive factors of pelvic lymph node metastasis in early-stage cervical cancer. *Oncol. Res. Treat.,* **2018**, *41*(4), 194-198. http://dx.doi.org/10.1159/000485840 PMID: 29562222

[18] Šarenac, T.; Mikov, M. Cervical cancer, different treatments and importance of bile acids as therapeutic agents in this disease. *Front Pharmacol,* **2019**, *10*, 484.

[19] Berek, J.S.; Matsuo, K.; Grubbs, B.H.; Gaffney, D.K.; Lee, S.I.; Kilcoyne, A.; Cheon, G.J.; Yoo, C.W.; Li, L.; Shao, Y.; Chen, T.; Kim, M.; Mikami, M. Multidisciplinary perspectives on newly revised 2018 FIGO staging of cancer of the cervix uteri. *J. Gynecol. Oncol.,* **2019**, *30*(2), e40. http://dx.doi.org/10.3802/jgo.2019.30.e40 PMID: 30740962

[20] Matsuo, K.; Machida, H.; Mandelbaum, R.S.; Konishi, I.; Mikami, M. Validation of the 2018 FIGO cervical cancer staging system. *Gynecol. Oncol.,* **2019**, *152*(1), 87-93. http://dx.doi.org/10.1016/j.ygyno.2018.10.026 PMID: 30389105

[21] Otero-García, M.M.; Mesa-Álvarez, A.; Nikolic, O.; Blanco-Lobato, P.; Basta-Nikolic, M.; de Llano-Ortega, R.M.; Paredes-Velázquez, L.; Nikolic, N.; Szewczyk-Bieda, M. Role of MRI in staging and follow-up of endometrial and cervical cancer: Pitfalls and mimickers. *Insights Imaging,* **2019**, *10*(1), 19. http://dx.doi.org/10.1186/s13244-019-0696-8 PMID: 30758678

[22] Balleyguier, C.; Sala, E.; Da Cunha, T.; Bergman, A.; Brkljacic, B.; Danza, F.; Forstner, R.; Hamm, B.; Kubik-Huch, R.; Lopez, C.; Manfredi, R.; McHugo, J.; Oleaga, L.; Togashi, K.; Kinkel, K. Staging of uterine cervical cancer with MRI: Guidelines of the European Society of Urogenital Radiology. *Eur. Radiol.,* **2011**, *21*(5), 1102-1110. http://dx.doi.org/10.1007/s00330-010-1998-x PMID: 21063710

[23] Valentini, A.L.; Gui, B.; Miccò, M.; Giuliani, M.; Rodolfino, E.; Ninivaggi, V.; Iacobucci, M.; Marino, M.; Gambacorta, M.A.; Testa, A.C.; Zannoni, G.F.; Bonomo, L. MRI anatomy of parametrial extension to better identify local pathways of disease spread in cervical cancer. *Diagn. Interv. Radiol.,* **2016**, *22*(4), 319-325. http://dx.doi.org/10.5152/dir.2015.15282 PMID: 27165471

[24] Hricak, H. MRI of the female pelvis: A review. *AJR Am. J. Roentgenol.,* **1986**, *146*(6), 1115-1122. http://dx.doi.org/10.2214/ajr.146.6.1115 PMID: 3486556

[25] Choi, H.J.; Ju, W.; Myung, S.K.; Kim, Y. Diagnostic performance of computer tomography, magnetic resonance imaging, and positron emission tomography or positron emission tomography/computer tomography for detection of metastatic lymph nodes in patients with cervical cancer: Meta□analysis. *Cancer Sci.,* **2010**, *101*(6), 1471-1479. http://dx.doi.org/10.1111/j.1349-7006.2010.01532.x PMID: 20298252

[26] Pannu, H.K.; Corl, F.M.; Fishman, E.K. CT evaluation of cervical cancer: Spectrum of disease. *Radiographics,* **2001**, *21*(5), 1155-1168. http://dx.doi.org/10.1148/radiographics.21.5.g01se311155 PMID: 11553823

[27] Wright, J.D.; Matsuo, K.; Huang, Y.; Tergas, A.I.; Hou, J.Y.; Khoury-Collado, F.; St Clair, C.M.; Ananth, C.V.; Neugut, A.I.; Hershman, D.L. Prognostic performance of the 2018 international federation of gynecology and obstetrics cervical cancer staging guidelines. *Obstet. Gynecol.,* **2019**, *134*(1), 49-57. http://dx.doi.org/10.1097/AOG.0000000000003311 PMID: 31188324

[28] Ayhan, A.; Aslan, K.; Öz, M.; Tohma, Y.A.; Kuşçu, E.; Meydanli, M.M. Para-aortic lymph node involvement revisited in the light of the revised 2018 FIGO staging system for cervical cancer. *Arch. Gynecol. Obstet.,* **2019**, *300*(3), 675-682. http://dx.doi.org/10.1007/s00404-019-05232-7 PMID: 31263988

[29] Nishio, S.; Matsuo, K.; Yonemoto, K.; Shimokawa, M.; Hosaka, M.; Kodama, M.; Miyake, T.M.; Ushijima, K.; Kamura, T.; Westin, S.N.; Soliman, P.T.; Coleman, R.L. Race and nodal disease status are prognostic factors in patients with stage IVB cervical cancer. *Oncotarget,* **2018**, *9*(64), 32321-32330. http://dx.doi.org/10.18632/oncotarget.25962 PMID: 30190789

[30] Rockall, A.G.; Ghosh, S.; Alexander-Sefre, F.; Babar, S.; Younis, M.T.S.; Naz, S.; Jacobs, I.J.; Reznek, R.H. Can MRI rule out bladder and rectal invasion in cervical cancer to help select patients for limited EUA? *Gynecol. Oncol.,* **2006**, *101*(2), 244-249. http://dx.doi.org/10.1016/j.ygyno.2005.10.012 PMID: 16310245

[31] Li, H.; Wu, X.; Cheng, X. Advances in diagnosis and treatment of metastatic cervical cancer. *J. Gynecol. Oncol.,* **2016**, *27*(4), e43. http://dx.doi.org/10.3802/jgo.2016.27.e43 PMID: 27171673

[32] Jain, M.A.; Limaiem, F. Cervical Squamous Cell Carcinoma. In: *StatPearls*; StatPearls Publishing, **2024**.

[33] Takeuchi, S. Biology and treatment of cervical adenocarcinoma. *Chin. J. Cancer Res.,* **2016**, *28*(2), 254-262. http://dx.doi.org/10.21147/j.issn.1000-9604.2016.02.11 PMID: 27198186

[34] Gien, L.T.; Beauchemin, M.C.; Thomas, G. Adenocarcinoma: A unique cervical cancer. *Gynecol. Oncol.,* **2010**, *116*(1), 140-146. http://dx.doi.org/10.1016/j.ygyno.2009.09.040 PMID: 19880165

[35] Stolnicu, S.; Hoang, L.; Hanko-Bauer, O.; Barsan, I.; Terinte, C.; Pesci, A.; Aviel-Ronen, S.; Kiyokawa, T.; Alvarado-Cabrero, I.; Oliva, E.; Park, K.J.; Soslow, R.A. Retracted article: Cervical adenosquamous carcinoma: detailed analysis of morphology, immunohistochemical profile, and clinical outcomes in 59 cases. *Mod. Pathol.,* **2019**, *32*(2), 269-279. http://dx.doi.org/10.1038/s41379-018-0123-6 PMID: 30258209

[36] Boustani, J.; Achkar, S.; Bertaut, A.; Genestie, C.; Gouy, S.; Pautier, P.; Morice, P.; Haie-Meder, C.; Chargari, C. Glassy cell carcinoma of the uterine cervix: 20-year experi-

ence from a comprehensive cancer center. *Cancer Radiother.,* **2021**, *25*(3), 207-212. http://dx.doi.org/10.1016/j.canrad.2020.07.007 PMID: 33408051

[37] Talerman, A.; Alenghat, E.; Okagaki, T. Glassy cell carcinoma of the uterine cervix. *APMIS,* **1991**, *Suppl 23*, 119-25.

[38] Tempfer, C.B.; Tischoff, I.; Dogan, A.; Hilal, Z.; Schultheis, B.; Kern, P.; Rezniczek, G.A. Neuroendocrine carcinoma of the cervix: A systematic review of the literature. *BMC Cancer,* **2018**, *18*(1), 530. http://dx.doi.org/10.1186/s12885-018-4447-x PMID: 29728073

[39] Kumar, T.; Nigam, J.S.; Kumari, M.; Swati, J.; Pandey, J. Cervical neuroendocrine carcinoma: A rare case report. *Cureus,* **2021**, *13*(6), e15532. http://dx.doi.org/10.7759/cureus.15532 PMID: 34269772

[40] Mirabello, L.; Clarke, M.; Nelson, C.; Dean, M.; Wentzensen, N.; Yeager, M.; Cullen, M.; Boland, J.; Schiffman, M.; Burk, R. The intersection of HPV epidemiology, genomics and mechanistic studies of HPV-mediated carcinogenesis. *Viruses,* **2018**, *10*(2), 80. http://dx.doi.org/10.3390/v10020080 PMID: 29438321

[41] Chen, A.A.; Gheit, T.; Franceschi, S.; Tommasino, M.; Clifford, G.M. Human papillomavirus 18 genetic variation and cervical cancer risk worldwide. *J. Virol.,* **2015**, *89*(20), 10680-10687. http://dx.doi.org/10.1128/JVI.01747-15 PMID: 26269181

[42] De Brot, L.; Pellegrini, B.; Moretti, S.T.; Carraro, D.M.; Soares, F.A.; Rocha, R.M.; Baiocchi, G.; da Cunha, I.W.; de Andrade, V.P. Infections with multiple high□risk HPV types are associated with high□grade and persistent low□-grade intraepithelial lesions of the cervix. *Cancer Cytopathol.,* **2017**, *125*(2), 138-143. http://dx.doi.org/10.1002/cncy.21789 PMID: 27870295

[43] Cornet, I.; Gheit, T.; Franceschi, S.; Vignat, J.; Burk, R.D.; Sylla, B.S.; Tommasino, M.; Clifford, G.M. Human papillomavirus type 16 genetic variants: Phylogeny and classification based on E6 and LCR. *J. Virol.,* **2012**, *86*(12), 6855-6861. http://dx.doi.org/10.1128/JVI.00483-12 PMID: 22491459

[44] Chen, A.A.; Heideman, D.A.M.; Boon, D.; Chen, Z.; Burk, R.D.; De Vuyst, H.; Gheit, T.; Snijders, P.J.F.; Tommasino, M.; Franceschi, S.; Clifford, G.M. Human papillomavirus 33 worldwide genetic variation and associated risk of cervical cancer. *Virology,* **2014**, *448*, 356-362. http://dx.doi.org/10.1016/j.virol.2013.10.033 PMID: 24314666

[45] Chen, A.A.; Heideman, D.A.M.; Boon, D.; Gheit, T.; Snijders, P.J.F.; Tommasino, M.; Franceschi, S.; Clifford, G.M. Human papillomavirus 45 genetic variation and cervical cancer risk worldwide. *J. Virol.,* **2014**, *88*(8), 4514-4521. http://dx.doi.org/10.1128/JVI.03534-13 PMID: 24501412

[46] Integrated genomic and molecular characterization of cervical cancer. *Nature,* **2017**, *543*(7645), 378-384. http://dx.doi.org/10.1038/nature21386 PMID: 28112728

[47] Henken, F.E.; Wilting, S.M.; Overmeer, R.M.; van Rietschoten, J.G.I.; Nygren, A.O.H.; Errami, A.; Schouten, J.P.; Meijer, C.J.L.M.; Snijders, P.J.F.; Steenbergen, R.D.M. Sequential gene promoter methylation during HPV-induced cervical carcinogenesis. *Br. J. Cancer,* **2007**, *97*(10), 1457-1464. http://dx.doi.org/10.1038/sj.bjc.6604055 PMID: 17971771

[48] Dong, S.M.; Kim, H.S.; Rha, S.H.; Sidransky, D. Promoter hypermethylation of multiple genes in carcinoma of the uterine cervix. *Clin. Cancer Res.,* **2001**, *7*(7), 1982-1986. PMID: 11448914

[49] Sartor, M.A.; Dolinoy, D.C.; Jones, T.R.; Colacino, J.A.; Prince, M.E.P.; Carey, T.E.; Rozek, L.S. Genome-wide methylation and expression differences in HPV(+) and HPV(-) squamous cell carcinoma cell lines are consistent with divergent mechanisms of carcinogenesis. *Epigenetics,* **2011**, *6*(6), 777-787. http://dx.doi.org/10.4161/epi.6.6.16216 PMID: 21613826

[50] Curty, G.; Menezes, A.N.; Brant, A.C.; de Mulder Rougvie, M.; Moreira, M.Â.M.; Soares, M.A. Expression of retroelements in cervical cancer and their interplay with HPV infection and host gene expression. *Cancers,* **2021**, *13*(14), 3513. http://dx.doi.org/10.3390/cancers13143513 PMID: 34298727

[51] Helt, A.M.; Funk, J.O.; Galloway, D.A. Inactivation of both the retinoblastoma tumor suppressor and p21 by the human papillomavirus type 16 E7 oncoprotein is necessary to inhibit cell cycle arrest in human epithelial cells. *J. Virol.,* **2002**, *76*(20), 10559-10568. http://dx.doi.org/10.1128/JVI.76.20.10559-10568.2002 PMID: 12239337

[52] Shin, M.K.; Balsitis, S.; Brake, T.; Lambert, P.F. Human papillomavirus E7 oncoprotein overrides the tumor suppressor activity of p21Cip1 in cervical carcinogenesis. *Cancer Res.,* **2009**, *69*(14), 5656-5663. http://dx.doi.org/10.1158/0008-5472.CAN-08-3711 PMID: 19584294

[53] Wijetunga, N.A.; Belbin, T.J.; Burk, R.D.; Whitney, K.; Abadi, M.; Greally, J.M.; Einstein, M.H.; Schlecht, N.F. Novel epigenetic changes in CDKN2A are associated with progression of cervical intraepithelial neoplasia. *Gynecol. Oncol.,* **2016**, *142*(3), 566-573. http://dx.doi.org/10.1016/j.ygyno.2016.07.006 PMID: 27401842

[54] McLaughlin-Drubin, M.E.; Park, D.; Munger, K. Tumor suppressor p16 ^{INK4A} is necessary for survival of cervical carcinoma cell lines. *Proc. Natl. Acad. Sci. USA,* **2013**, *110*(40), 16175-16180. http://dx.doi.org/10.1073/pnas.1310432110 PMID: 24046371

[55] Karim, R.; Meyers, C.; Backendorf, C.; Ludigs, K.; Offringa, R.; van Ommen, G.J.B.; Melief, C.J.M.; van der Burg, S.H.; Boer, J.M. Human papillomavirus deregulates the response of a cellular network comprising of chemotactic and proinflammatory genes. *PLoS One,* **2011**, *6*(3), e17848. http://dx.doi.org/10.1371/journal.pone.0017848 PMID: 21423754

[56] Agarwal, S.M.; Raghav, D.; Singh, H.; Raghava, G.P.S. CCDB: A curated database of genes involved in cervix cancer. *Nucleic Acids Res.,* **2011**, *39*(Database)(Suppl. 1), D975-D979. http://dx.doi.org/10.1093/nar/gkq1024 PMID: 21045064

[57] Ngo, C.; Samuels, S.; Bagrintseva, K.; Slocker, A.; Hupé, P.; Kenter, G.; Popovic, M.; Samet, N.; Tresca, P.; von der Leyen, H.; Deutsch, E.; Rouzier, R.; Belin, L.; Kamal, M.; Scholl, S. From prospective biobanking to precision medicine: BIO-RAIDs – An EU study protocol in cervical cancer. *BMC Cancer,* **2015**, *15*(1), 842. http://dx.doi.org/10.1186/s12885-015-1801-0 PMID: 26531748

[58] Sangwaiya, A.; Gill, M.; Bairwa, S.; Chaudhry, M.; Sen,

R.; Prakash Kataria, S. Utility of P16/INK4a and Ki-67 in preneoplasticand neoplastic lesions of cervix. *Iran. J. Pathol.,* **2018**, *13*(3), 308-316.
PMID: 30636953

[59] Gonçalves, J.E.S.; Andrade, C.V.; Russomano, F.B.; Nuovo, G.J.; Amaro-Filho, S.M.; Carvalho, M.O.O.; Nicol, A.F. The role of p16 as putative biomarker for cervical neoplasia: A controversial issue? *MedicalExpress,* **2017**, *4*(6), 4.
http://dx.doi.org/10.5935/MedicalExpress.2017.06.01

[60] McCluggage, W.G. Immunohistochemical and functional biomarkers of value in female genital tract lesions. *Int. J. Gynecol. Pathol.,* **2006**, *25*(2), 101-120.
http://dx.doi.org/10.1097/01.pgp.0000192269.14666.68 PMID: 16633059

[61] Chen, G.; Wei, K.; Ling, Y.; Su, S.; Zhu, M.; Chen, G. The prognostic role of Ki-67/MIB-1 in cervical cancer: A systematic review with meta-analysis. *Med. Sci. Monit.,* **2015**, *21*, 882-889.
http://dx.doi.org/10.12659/MSM.892807 PMID: 25807305

[62] Cavalcante, J.; Sampaio, J.; Filho, J.; Vieira, R.; Eleutério, J.; Lima, R.; Ribeiro, R.; Almeida, P. Progressive loss of E-cadherin immunoexpression during cervical carcinogenesis. *Acta Cirurgica Brasileira,* **2014**, *29*, 667-674.

[63] Ma, X.; Ge, A.; Han, J.; Kang, J.; Zhang, Y.; Liu, X.; Xing, L.; Liu, X.; Dong, L. Meta-analysis of downregulated E-cadherin as a diagnostic biomarker for cervical cancer. *Arch. Gynecol. Obstet.,* **2022**, *307*(2), 331-341.
http://dx.doi.org/10.1007/s00404-022-06475-7 PMID: 35279729

[64] Shah, U.J.; Nasiruddin, M.; Dar, S.A.; Khan, M.K.A.; Akhter, M.R.; Singh, N.; Rabaan, A.A.; Haque, S. Emerging biomarkers and clinical significance of HPV genotyping in prevention and management of cervical cancer. *Microb. Pathog.,* **2020**, *143*, 104131.
http://dx.doi.org/10.1016/j.micpath.2020.104131 PMID: 32169490

[65] Vieillard, V.; Paul, M. Physicochemical stability study of a biosimilar of Bevacizumab in vials and after dilution in 0.9% NaCl in polyolefin intravenous bags. *Pharm. Technol. Hosp. Pharm.,* **2023**, *8*(1), 20220007.
http://dx.doi.org/10.1515/pthp-2022-0007

[66] Garcia, J.; Hurwitz, H.I.; Sandler, A.B.; Miles, D.; Coleman, R.L.; Deurloo, R.; Chinot, O.L. Bevacizumab (Avastin®) in cancer treatment: A review of 15 years of clinical experience and future outlook. *Cancer Treat. Rev.,* **2020**, *86*, 102017.
http://dx.doi.org/10.1016/j.ctrv.2020.102017 PMID: 32335505

[67] Saini, J.; Bansal, V.; Chandra, A.; Madan, J.; Jain, U.K.; Chandra, R.; Jain, S.M. Bleomycin sulphate loaded nanostructured lipid particles augment oral bioavailability, cytotoxicity and apoptosis in cervical cancer cells. *Colloids Surf. B Biointerfaces,* **2014**, *118*, 101-110.
http://dx.doi.org/10.1016/j.colsurfb.2014.03.036 PMID: 24732397

[68] Colombo, N.; Dubot, C.; Lorusso, D.; Caceres, M.V.; Hasegawa, K.; Shapira-Frommer, R.; Tewari, K.S.; Salman, P.; Hoyos Usta, E.; Yañez, E.; Gümüş, M.; Olivera Hurtado de Mendoza, M.; Samouëlian, V.; Castonguay, V.; Arkhipov, A.; Toker, S.; Li, K.; Keefe, S.M.; Monk, B.J. Pembrolizumab for persistent, recurrent, or metastatic cervical cancer. *N. Engl. J. Med.,* **2021**, *385*(20), 1856-1867.
http://dx.doi.org/10.1056/NEJMoa2112435 PMID: 34534429

[69] Agostinelli, V.; Musacchio, L.; Camarda, F.; Salutari, V.; Carbone, M.V.; Ghizzoni, V.; Nero, C.; Ricci, C.; Perri, M.T.; Giudice, E.; Lardino, S.; Berardi, R.; Scambia, G.; Lorusso, D. Therapeutic potential of tisotumab vedotin in the treatment of recurrent or metastatic cervical cancer: A short report on the emerging data. *Cancer Manag. Res.,* **2023**, *15*, 1063-1072.
http://dx.doi.org/10.2147/CMAR.S294080 PMID: 37790898

[70] Sachan, P.L.; Singh, M.; Patel, M.L.; Sachan, R. A study on cervical cancer screening using pap smear test and clinical correlation. *Asia Pac. J. Oncol. Nurs.,* **2018**, *5*(3), 337-341.
http://dx.doi.org/10.4103/apjon.apjon_15_18 PMID: 29963597

[71] Burness, J.V.; Schroeder, J.M.; Warren, J.B. Cervical colposcopy: Indications and risk assessment. *Am. Fam. Physician,* **2020**, *102*(1), 39-48.
PMID: 32603071

[72] Valls, J.; Baena, A.; Venegas, G.; Celis, M.; González, M.; Sosa, C.; Santin, J.L.; Ortega, M.; Soilán, A.; Turcios, E.; Figueroa, J.; Rodríguez de la Peña, M.; Figueredo, A.; Beracochea, A.V.; Pérez, N.; Martínez-Better, J.; Lora, O.; Jiménez, J.Y.; Giménez, D.; Fleider, L.; Salgado, Y.; Martínez, S.; Bellido-Fuentes, Y.; Flores, B.; Tatti, S.; Villagra, V.; Cruz-Valdez, A.; Terán, C.; Sánchez, G.I.; Rodríguez, G.; Picconi, M.A.; Ferrera, A.; Mendoza, L.; Calderón, A.; Murillo, R.; Wiesner, C.; Broutet, N.; Luciani, S.; Pérez, C.; Darragh, T.M.; Jerónimo, J.; Herrero, R.; Almonte, M. Performance of standardised colposcopy to detect cervical precancer and cancer for triage of women testing positive for human papillomavirus: Results from the ESTAMPA multicentric screening study. *Lancet Glob. Health,* **2023**, *11*(3), e350-e360.
http://dx.doi.org/10.1016/S2214-109X(22)00545-9 PMID: 36796982

[73] Oguntayo, A.O. The role of punch biopsy in the management of carcinoma of the cervix in a low resource centre. *Open J. Clin. Diagn.,* **2013**, *3*(4), 171-172.
http://dx.doi.org/10.4236/ojcd.2013.34031

[74] Gage, J.C.; Duggan, M.A.; Nation, J.G.; Gao, S.; Castle, P.E. Detection of cervical cancer and its precursors by endocervical curettage in 13,115 colposcopically guided biopsy examinations. *Am J Obstet Gynecol,* **2010**, *203*(5), 481.

[75] Massad, L.S.; Perkins, R.B.; Naresh, A.; Nelson, E.L.; Spiryda, L.; Gecsi, K.S.; Mulhem, E.; Kostas-Polston, E.; Zou, T.; Giles, T.L.; Wentzensen, N. Colposcopy standards: Guidelines for endocervical curettage at colposcopy. *J. Low. Genit. Tract Dis.,* **2023**, *27*(1), 97-101.
PMID: 36222824

[76] Abraham, C.; Kim, R.; Oner, C.; Bucknor, A. Colposcopy and loop electrosurgical excision procedure: A simulated exercise. *MedEdPORTAL,* **2023**, *19*, 11344.
http://dx.doi.org/10.15766/mep_2374-8265.11344 PMID: 37691878

[77] Yang, E.J.; Kim, N.R.; Choi, J.Y.; Kim, W.Y.; Lee, S.J. Loop electrosurgical excision procedure combined with cold coagulation for cervical intraepithelial neoplasia and adenocarcinoma in-situ: A feasible treatment with a low risk of residual/recurrent disease. *Infect. Agent. Cancer,* **2020**, *15*(1), 58.
http://dx.doi.org/10.1186/s13027-020-00326-3 PMID: 33042214

[78] Chiva, L.; Chacon, E. Is conization a protective surgical maneuver in early cervical cancer? *Ann. Surg. Oncol.,*

2021, *28*(7), 3463-3464. http://dx.doi.org/10.1245/s10434-021-09705-5 PMID: 33730225

[79] Nica, A.; Covens, A. Cone biopsy (with pelvic lymphadenectomy) for fertility preservation in early stage cervical cancer: Ready for prime time? *Gynecol. Oncol.,* **2020**, *158*(2), 229-230. http://dx.doi.org/10.1016/j.ygyno.2020.07.003 PMID: 32778250

[80] Klapdor, R.; Hertel, H.; Delebinski, L.; Hillemanns, P. Association of preoperative cone biopsy with recurrences after radical hysterectomy. *Arch. Gynecol. Obstet.,* **2022**, *305*(1), 215-222. http://dx.doi.org/10.1007/s00404-021-06145-0 PMID: 34291339

[81] Bourgioti, C.; Chatoupis, K.; Moulopoulos, L.A. Current imaging strategies for the evaluation of uterine cervical cancer. *World J. Radiol.,* **2016**, *8*(4), 342-354. http://dx.doi.org/10.4329/wjr.v8.i4.342 PMID: 27158421

[82] Poli, U.; Bidinger, P.D.; Gowrishankar, S. Visual inspection with acetic acid (*via*) screening program: 7 years experience in early detection of cervical cancer and pre-cancers in rural South India. *Indian J. Community Med.,* **2015**, *40*(3), 203-207. http://dx.doi.org/10.4103/0970-0218.158873 PMID: 26170547

[83] Smith, E.S.; Moon, A.S.; O'Hanlon, R.; Leitao, M.M., Jr; Sonoda, Y.; Abu-Rustum, N.R.; Mueller, J.J. Radical trachelectomy for the treatment of early-stage cervical cancer. *Obstet. Gynecol.,* **2020**, *136*(3), 533-542. http://dx.doi.org/10.1097/AOG.0000000000003952 PMID: 32769648

[84] Ramirez, P.T.; Frumovitz, M.; Pareja, R.; Lopez, A.; Vieira, M.; Ribeiro, R.; Buda, A.; Yan, X.; Shuzhong, Y.; Chetty, N.; Isla, D.; Tamura, M.; Zhu, T.; Robledo, K.P.; Gebski, V.; Asher, R.; Behan, V.; Nicklin, J.L.; Coleman, R.L.; Obermair, A. Minimally invasive *versus* abdominal radical hysterectomy for cervical cancer. *N. Engl. J. Med.,* **2018**, *379*(20), 1895-1904. http://dx.doi.org/10.1056/NEJMoa1806395 PMID: 30380365

[85] Yang, J.; Cai, H.; Xiao, Z.X.; Wang, H.; Yang, P. Effect of radiotherapy on the survival of cervical cancer patients. *Medicine,* **2019**, *98*(30), e16421. http://dx.doi.org/10.1097/MD.0000000000016421 PMID: 31348242

[86] Chao, J.; Silin, L.; Che, W.; Jie, C.; Jin, W.; Xinyue, Z.; Jinlu, M.; Mengjiao, C. Relationship between visceral obesity and prognosis in patients with stage IVB cervical cancer receiving radiotherapy and chemotherapy. *Cancer Pathog Ther.,* **2023**, *2*(3), 180-186.

[87] Feng, X.; Meng, X.; Tang, D.; Guo, S.; Liao, Q.; Chen, J.; Xie, Q.; Liu, F.; Fang, Y.; Sun, C.; Han, Y.; Ai, J.; Li, K. Reversal of the immunosuppressive tumor microenvironment *via* platinum-based neoadjuvant chemotherapy in cervical cancer. *Cancer Pathogenesis and Therapy,* **2024**, *2*(1), 38-49. http://dx.doi.org/10.1016/j.cpt.2023.07.003 PMID: 38328710

[88] Huang, Z.; Yao, W.; Zhong, Z.; Yang, G.; Liu, J.; Gu, H.; Huang, J. Chemotherapy alone *versus* chemotherapy plus ^{125}I brachytherapy for the second-line treatment of locally recurrent cervical cancer after/with radical treatment: A propensity score analysis. *Heliyon,* **2024**, *10*(2), e24666. http://dx.doi.org/10.1016/j.heliyon.2024.e24666 PMID: 38298696

[89] Tsuda, N.; Watari, H.; Ushijima, K. Chemotherapy and molecular targeting therapy for recurrent cervical cancer. *Chin. J. Cancer Res.,* **2016**, *28*(2), 241-253. http://dx.doi.org/10.21147/j.issn.1000-9604.2016.02.14 PMID: 27199523

[90] Gawde, K.A.; Sau, S.; Tatiparti, K.; Kashaw, S.K.; Mehrmohammadi, M.; Azmi, A.S.; Iyer, A.K. Paclitaxel and difluorinated curcumin loaded in albumin nanoparticles for targeted synergistic combination therapy of ovarian and cervical cancers. *Colloids Surf. B Biointerfaces,* **2018**, *167*, 8-19. http://dx.doi.org/10.1016/j.colsurfb.2018.03.046 PMID: 29625422

[91] Mahalakshmi, M.; Kumar, P. Phloroglucinol-conjugated gold nanoparticles targeting mitochondrial membrane potential of human cervical (HeLa) cancer cell lines. *Spectrochim. Acta A Mol. Biomol. Spectrosc.,* **2019**, *219*, 450-456. http://dx.doi.org/10.1016/j.saa.2019.04.060 PMID: 31063960

[92] Jia, Y.; Huang, X.; Li, S.; Wu, Y.; Wu, J.; Duan, Z.; Luo, M.; Tang, J. Engineering of surface-altered polydopamine nanocomposites for successive drug release and *in vivo* antitumor effects in cervical cancer therapy: Investigation of antiproliferative effects and apoptosis. *J. Drug Deliv. Sci. Technol.,* **2024**, *91*, 105189. http://dx.doi.org/10.1016/j.jddst.2023.105189

[93] Nascimento, J.; do Canto Olegário, I.; Mariot, C.; de Oliveira, T.V.; dos Santos Chaves, P.; Oliveira, R.; de Oliveira, E.G.; Guterres, S.S.; Buffon, A.; Pilger, D.A.; Beck, R.C.R. Encapsulation of orlistat in biodegradable polymeric nanocapsules improves its cytotoxic effect against cervical cancer cells. *J. Drug Deliv. Sci. Technol.,* **2023**, *89*, 105086. http://dx.doi.org/10.1016/j.jddst.2023.105086

[94] Tomao, S.; Tomao, F.; Rossi, L.; Zaccarelli, E.; Caruso, D.; Zoratto, F.; Benedetti Panici, P.; Papa, A. Angiogenesis and antiangiogenic agents in cervical cancer. *OncoTargets Ther.,* **2014**, *7*, 2237-2248. http://dx.doi.org/10.2147/OTT.S68286 PMID: 25506227

[95] Cohen, A.C.; Roane, B.M.; Leath, C.A., III Novel therapeutics for recurrent cervical cancer: Moving towards personalized therapy. *Drugs,* **2020**, *80*(3), 217-227. http://dx.doi.org/10.1007/s40265-019-01249-z PMID: 31939072

[96] Monk, B.J.; Mas Lopez, L.; Zarba, J.J.; Oaknin, A.; Tarpin, C.; Termrungruanglert, W.; Alber, J.A.; Ding, J.; Stutts, M.W.; Pandite, L.N. Phase II, open-label study of pazopanib or lapatinib monotherapy compared with pazopanib plus lapatinib combination therapy in patients with advanced and recurrent cervical cancer. *J. Clin. Oncol.,* **2010**, *28*(22), 3562-3569. http://dx.doi.org/10.1200/JCO.2009.26.9571 PMID: 20606083

[97] Chan, J.K.; Deng, W.; Higgins, R.V.; Tewari, K.S.; Bonebrake, A.J.; Hicks, M.; Gaillard, S.; Ramirez, P.T.; Chafe, W.; Monk, B.J.; Aghajanian, C. A phase II evaluation of brivanib in the treatment of persistent or recurrent carcinoma of the cervix: An NRG Oncology/Gynecologic Oncology Group study. *Gynecol. Oncol.,* **2017**, *146*(3), 554-559. http://dx.doi.org/10.1016/j.ygyno.2017.05.033 PMID: 28728751

[98] Liu, Z.; Chen, H.; Lv, F.; Wang, J.; Zhao, S.; Li, Y.; Xue, X.; Liu, Y.; Wei, G.; Lu, W. Sequential release of paclitax-

el and imatinib from core–shell microparticles prepared by coaxial electrospray for vaginal therapy of cervical cancer. *Int. J. Mol. Sci.,* **2021**, *22*(16), 8760. http://dx.doi.org/10.3390/ijms22168760 PMID: 34445466

[99] Candelaria, M.; Arias-Bonfill, D.; Chávez-Blanco, A.; Chanona, J.; Cantú, D.; Pérez, C.; Dueñas-González, A. Lack in efficacy for imatinib mesylate as second-line treatment of recurrent or metastatic cervical cancer expressing platelet-derived growth factor receptor alpha. *Int. J. Gynecol. Cancer,* **2009**, *19*(9), 1632-1637. http://dx.doi.org/10.1111/IGC.0b013e3181a80bb5 PMID: 19955950

[100] Eskander, R.N.; Tewari, K.S. Targeting angiogenesis in advanced cervical cancer. *Ther. Adv. Med. Oncol.,* **2014**, *6*(6), 280-292. http://dx.doi.org/10.1177/1758834014543794 PMID: 25364393

[101] Kagabu, M.; Nagasawa, T.; Sato, C.; Fukagawa, Y.; Kawamura, H.; Tomabechi, H.; Takemoto, S.; Shoji, T.; Baba, T. Immunotherapy for uterine cervical cancer using checkpoint inhibitors: Future directions. *Int. J. Mol. Sci.,* **2020**, *21*(7), 2335. http://dx.doi.org/10.3390/ijms21072335 PMID: 32230938

[102] Peralta-Zaragoza, O.; Bermúdez-Morales, V.H.; Pérez--Plasencia, C.; Salazar-León, J.; Gómez-Cerón, C.; Madrid--Marina, V. Targeted treatments for cervical cancer: A review. *OncoTargets Ther.,* **2012**, *5*, 315-328. http://dx.doi.org/10.2147/OTT.S25123 PMID: 23144564

[103] Jazaeri, A.A.; Zsiros, E.; Amaria, R.N.; Artz, A.S.; Edwards, R.P.; Wenham, R.M.; Slomovitz, B.M.; Walther, A.; Thomas, S.S.; Chesney, J.A.; Morris, R.; Matsuo, K.; Gaillard, S.; Rose, P.G.; Donas, J.G.; Tromp, J.M.; Tavakkoli, F.; Li, H.; Fardis, M.; Monk, B.J. Safety and efficacy of adoptive cell transfer using autologous tumor infiltrating lymphocytes (LN-145) for treatment of recurrent, metastatic, or persistent cervical carcinoma. *J. Clin. Oncol.,* **2019**, *37*(15_suppl)(Suppl.), 2538-2538. http://dx.doi.org/10.1200/JCO.2019.37.15_suppl.2538

[104] Kenter, G.G.; Welters, M.J.P.; Valentijn, A.R.P.M.; Lowik, M.J.G.; Berends-van der Meer, D.M.A.; Vloon, A.P.G.; Essahsah, F.; Fathers, L.M.; Offringa, R.; Drijfhout, J.W.; Wafelman, A.R.; Oostendorp, J.; Fleuren, G.J.; van der Burg, S.H.; Melief, C.J.M. Vaccination against HPV-16 oncoproteins for vulvar intraepithelial neoplasia. *N. Engl. J. Med.,* **2009**, *361*(19), 1838-1847. http://dx.doi.org/10.1056/NEJMoa0810097 PMID: 19890126

[105] Eskander, R.N.; Tewari, K.S. Immunotherapy: An evolving paradigm in the treatment of advanced cervical cancer. *Clin. Ther.,* **2015**, *37*(1), 20-38. http://dx.doi.org/10.1016/j.clinthera.2014.11.010 PMID: 25592089

[106] Emens, L.A.; Ascierto, P.A.; Darcy, P.K.; Demaria, S.; Eggermont, A.M.M.; Redmond, W.L.; Seliger, B.; Marincola, F.M. Cancer immunotherapy: Opportunities and challenges in the rapidly evolving clinical landscape. *Eur. J. Cancer,* **2017**, *81*, 116-129. http://dx.doi.org/10.1016/j.ejca.2017.01.035 PMID: 28623775

[107] Enwere, E.K.; Kornaga, E.N.; Dean, M.; Koulis, T.A.; Phan, T.; Kalantarian, M.; Köbel, M.; Ghatage, P.; Magliocco, A.M.; Lees-Miller, S.P.; Doll, C.M. Expression of PD-L1 and presence of CD8-positive T cells in pretreatment specimens of locally advanced cervical cancer. *Mod. Pathol.,* **2017**, *30*(4), 577-586. http://dx.doi.org/10.1038/modpathol.2016.221 PMID: 28059093

[108] Reddy, O.L.; Shintaku, P.I.; Moatamed, N.A. Programmed death-ligand 1 (PD-L1) is expressed in a significant number of the uterine cervical carcinomas. *Diagn. Pathol.,* **2017**, *12*(1), 45. http://dx.doi.org/10.1186/s13000-017-0631-6 PMID: 28623908

[109] Mezache, L.; Paniccia, B.; Nyinawabera, A.; Nuovo, G.J. Enhanced expression of PD L1 in cervical intraepithelial neoplasia and cervical cancers. *Mod. Pathol.,* **2015**, *28*(12), 1594-1602. http://dx.doi.org/10.1038/modpathol.2015.108 PMID: 26403783

[110] Browne, I.; Fennelly, D.W.; Crown, J.; Murray, H. The efficacy and safety of pembrolizumab in advanced cervical cancer—A real world treatment study in an irish healthcare setting. *J. Clin. Oncol.,* **2020**, *38*(15_suppl)(Suppl.), e18007-e18007. http://dx.doi.org/10.1200/JCO.2020.38.15_suppl.e18007

[111] Frenel, J.S.; Le Tourneau, C.; O'Neil, B.; Ott, P.A.; Piha--Paul, S.A.; Gomez-Roca, C.; van Brummelen, E.M.J.; Rugo, H.S.; Thomas, S.; Saraf, S.; Rangwala, R.; Varga, A. Safety and efficacy of pembrolizumab in advanced, programmed death ligand 1–positive cervical cancer: Results from the phase Ib KEYNOTE-028 trial. *J. Clin. Oncol.,* **2017**, *35*(36), 4035-4041. http://dx.doi.org/10.1200/JCO.2017.74.5471 PMID: 29095678

[112] Naumann, R.W.; Hollebecque, A.; Meyer, T.; Devlin, M.J.; Oaknin, A.; Kerger, J.; López-Picazo, J.M.; Machiels, J.P.; Delord, J.P.; Evans, T.R.J.; Boni, V.; Calvo, E.; Topalian, S.L.; Chen, T.; Soumaoro, I.; Li, B.; Gu, J.; Zwirtes, R.; Moore, K.N. Safety and efficacy of nivolumab monotherapy in recurrent or metastatic cervical, vaginal, or vulvar carcinoma: Results from the phase I/II checkmate 358 trial. *J. Clin. Oncol.,* **2019**, *37*(31), 2825-2834. http://dx.doi.org/10.1200/JCO.19.00739 PMID: 31487218

[113] Leach, D.R.; Krummel, M.F.; Allison, J.P. Enhancement of antitumor immunity by CTLA-4 blockade. *Science,* **1996**, *271*(5256), 1734-1736. http://dx.doi.org/10.1126/science.271.5256.1734 PMID: 8596936

[114] Duranti, S.; Pietragalla, A.; Daniele, G.; Nero, C.; Ciccarone, F.; Scambia, G.; Lorusso, D. Role of immune checkpoint inhibitors in cervical cancer: From preclinical to clinical data. *Cancers,* **2021**, *13*(9), 2089. http://dx.doi.org/10.3390/cancers13092089 PMID: 33925884

[115] Lheureux, S.; Butler, M.O.; Clarke, B.; Cristea, M.C.; Martin, L.P.; Tonkin, K.; Fleming, G.F.; Tinker, A.V.; Hirte, H.W.; Tsoref, D.; Mackay, H.; Dhani, N.C.; Ghatage, P.; Weberpals, J.; Welch, S.; Pham, N.A.; Motta, V.; Sotov, V.; Wang, L.; Karakasis, K.; Udagani, S.; Kamel-Reid, S.; Streicher, H.Z.; Shaw, P.; Oza, A.M. Association of ipilimumab with safety and antitumor activity in women with metastatic or recurrent human papillomavirus–related cervical carcinoma. *JAMA Oncol.,* **2018**, *4*(7), e173776. http://dx.doi.org/10.1001/jamaoncol.2017.3776 PMID: 29145543

[116] Naumann, R.W.; Oaknin, A.; Meyer, T.; Lopez-Picazo, J.M.; Lao, C.; Bang, Y.J.; Boni, V.; Sharfman, W.H.; Park, J.C.; Devriese, L.A.; Harano, K.; Chung, C.H.; Topalian, S.L.; Zaki, K.; Chen, T.; Gu, J.; Li, B.; Barrows, A.; Hor-

vath, A.; Moore, K.N. Efficacy and safety of nivolumab (Nivo) + ipilimumab (Ipi) in patients (pts) with recurrent/metastatic (R/M) cervical cancer: Results from CheckMate 358. *Ann. Oncol.,* **2019**, *30*, v898-v899. http://dx.doi.org/10.1093/annonc/mdz394.059

[117] Da Silva, D.M.; Enserro, D.M.; Mayadev, J.S.; Skeate, J.G.; Matsuo, K.; Pham, H.Q.; Lankes, H.A.; Moxley, K.M.; Ghamande, S.A.; Lin, Y.G.; Schilder, R.J.; Birrer, M.J.; Kast, W.M. Immune activation in patients with locally advanced cervical cancer treated with ipilimumab following definitive chemoradiation (GOG-9929). *Clin. Cancer Res.,* **2020**, *26*(21), 5621-5630. http://dx.doi.org/10.1158/1078-0432.CCR-20-0776 PMID: 32816895

[118] Mauricio, D.; Zeybek, B.; Tymon-Rosario, J.; Harold, J.; Santin, A.D. Immunotherapy in cervical cancer. *Curr. Oncol. Rep.,* **2021**, *23*(6), 61. http://dx.doi.org/10.1007/s11912-021-01052-8 PMID: 33852056

[119] Geukes Foppen, M.H.; Donia, M.; Svane, I.M.; Haanen, J.B.A.G. Tumor□infiltrating lymphocytes for the treatment of metastatic cancer. *Mol. Oncol.,* **2015**, *9*(10), 1918-1935. http://dx.doi.org/10.1016/j.molonc.2015.10.018 PMID: 26578452

[120] Wrzesinski, C.; Restifo, N.P. Less is more: Lymphodepletion followed by hematopoietic stem cell transplant augments adoptive T-cell-based anti-tumor immunotherapy. *Curr. Opin. Immunol.,* **2005**, *17*(2), 195-201. http://dx.doi.org/10.1016/j.coi.2005.02.002 PMID: 15766681

[121] Stevanović, S.; Draper, L.M.; Langhan, M.M.; Campbell, T.E.; Kwong, M.L.; Wunderlich, J.R.; Dudley, M.E.; Yang, J.C.; Sherry, R.M.; Kammula, U.S.; Restifo, N.P.; Rosenberg, S.A.; Hinrichs, C.S. Complete regression of metastatic cervical cancer after treatment with human papillomavirus-targeted tumor-infiltrating T cells. *J. Clin. Oncol.,* **2015**, *33*(14), 1543-1550. http://dx.doi.org/10.1200/JCO.2014.58.9093 PMID: 25823737

[122] Liao, J.B. Immunotherapy for gynecologic cancers. *Gynecol. Oncol.,* **2016**, *142*(1), 3-5. http://dx.doi.org/10.1016/j.ygyno.2016.05.029 PMID: 27242186

[123] Basu, P.; Mehta, A.; Jain, M.; Gupta, S.; Nagarkar, R.V.; John, S.; Petit, R. A randomized phase 2 study of ADXS11-001 listeria monocytogenes–listeriolysin o immunotherapy with or without cisplatin in treatment of advanced cervical cancer. *Int. J. Gynecol. Cancer,* **2018**, *28*(4), 764-772. http://dx.doi.org/10.1097/IGC.0000000000001235 PMID: 29538258

[124] Borysiewicz, L.K.; Fiander, A.; Nimako, M.; Man, S.; Wilkinson, G.W.G.; Westmoreland, D.; Evans, A.S.; Adams, M.; Stacey, S.N.; Boursnell, M.E.G.; Rutherford, E.; Hickling, J.K.; Inglis, S.C. A recombinant vaccinia virus encoding human papillomavirus types 16 and 18, E6 and E7 proteins as immunotherapy for cervical cancer. *Lancet,* **1996**, *347*(9014), 1523-1527. http://dx.doi.org/10.1016/S0140-6736(96)90674-1 PMID: 8684105

[125] Kaufmann, A.M.; Stern, P.L.; Rankin, E.M.; Sommer, H.; Nuessler, V.; Schneider, A.; Adams, M.; Onon, T.S.; Bauknecht, T.; Wagner, U.; Kroon, K.; Hickling, J.; Boswell, C.M.; Stacey, S.N.; Kitchener, H.C.; Gillard, J.; Wanders, J.; Roberts, J.S.; Zwierzina, H. Safety and immunogenicity of TA-HPV, a recombinant vaccinia virus expressing modified human papillomavirus (HPV)-16 and HPV-18 E6 and E7 genes, in women with progressive cervical cancer. *Clin. Cancer Res.,* **2002**, *8*(12), 3676-3685. PMID: 12473576

[126] Roman, L.D.; Wilczynski, S.; Muderspach, L.I.; Burnett, A.F.; O'Meara, A.; Brinkman, J.A.; Kast, W.M.; Facio, G.; Felix, J.C.; Aldana, M.; Weber, J.S. A phase II study of Hsp-7 (SGN-00101) in women with high-grade cervical intraepithelial neoplasia. *Gynecol. Oncol.,* **2007**, *106*(3), 558-566. http://dx.doi.org/10.1016/j.ygyno.2007.05.038 PMID: 17631950

[127] Garcia, F.; Petry, K.U.; Muderspach, L.; Gold, M.A.; Braly, P.; Crum, C.P.; Magill, M.; Silverman, M.; Urban, R.G.; Hedley, M.L.; Beach, K.J. ZYC101a for treatment of high-grade cervical intraepithelial neoplasia: A randomized controlled trial. *Obstet. Gynecol.,* **2004**, *103*(2), 317-326. http://dx.doi.org/10.1097/01.AOG.0000110246.93627.17 PMID: 14754702

[128] Trimble, C.L.; Morrow, M.P.; Kraynyak, K.A.; Shen, X.; Dallas, M.; Yan, J.; Edwards, L.; Parker, R.L.; Denny, L.; Giffear, M.; Brown, A.S.; Marcozzi-Pierce, K.; Shah, D.; Slager, A.M.; Sylvester, A.J.; Khan, A.; Broderick, K.E.; Juba, R.J.; Herring, T.A.; Boyer, J.; Lee, J.; Sardesai, N.Y.; Weiner, D.B.; Bagarazzi, M.L. Safety, efficacy, and immunogenicity of VGX-3100, a therapeutic synthetic DNA vaccine targeting human papillomavirus 16 and 18 E6 and E7 proteins for cervical intraepithelial neoplasia 2/3: A randomised, double-blind, placebo-controlled phase 2b trial. *Lancet,* **2015**, *386*(10008), 2078-2088. http://dx.doi.org/10.1016/S0140-6736(15)00239-1 PMID: 26386540

[129] Rischin, D.; Gil-Martin, M.; González-Martin, A.; Braña, I.; Hou, J.Y.; Cho, D.; Falchook, G.S.; Formenti, S.; Jabbour, S.; Moore, K.; Naing, A.; Papadopoulos, K.P.; Baranda, J.; Fury, W.; Feng, M.; Stankevich, E.; Li, J.; Yama--Dang, N.A.; Yoo, S.Y.; Lowy, I.; Mathias, M.; Fury, M.G. PD-1 blockade in recurrent or metastatic cervical cancer: Data from cemiplimab phase I expansion cohorts and characterization of PD-L1 expression in cervical cancer. *Gynecol. Oncol.,* **2020**, *159*(2), 322-328. http://dx.doi.org/10.1016/j.ygyno.2020.08.026 PMID: 32917410

[130] O'Malley, D.M.; Oaknin, A.; Monk, B.J.; Selle, F.; Rojas, C.; Gladieff, L.; Berton, D.; Leary, A.; Moore, K.N.; Estevez-Diz, M.D.P.; Hardy-Bessard, A.C.; Alexandre, J.; Opperman, C.P.; de Azevedo, C.R.A.S.; Randall, L.M.; Feliu, W.O.; Ancukiewicz, M.; Ray-Coquard, I. Phase II study of the safety and efficacy of the anti-PD-1 antibody balstilimab in patients with recurrent and/or metastatic cervical cancer. *Gynecol. Oncol.,* **2021**, *163*(2), 274-280. http://dx.doi.org/10.1016/j.ygyno.2021.08.018 PMID: 34452745