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The Scenario of Recurrence of Cervical Cancer by Epigenetics

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Abstract: ***Epigenetic changes happen all the time during life, however, some differences are responsible for specific diseases. One such disease is cancer; nevertheless, a cancer recurrence can be exceedingly lethal and hasten the demise process. Epigenetic changes have the power to completely rule out all current modalities of treatment and have a rapid and substantial impact on the recurrence of cancer.***
Research indicates that recurrences may occur in up to 70% of individuals with stage III to IVB of cervical cancer. Even with extensive therapy, the 5-year overall survival (OS) rate for recurrent cervical cancer is less than 5%, and the disease is still extremely difficult to treat. This is particularly true for those who experience recurrence in a region that has previously undergone radiation treatment. Therefore, it is important to comprehend the role that epigenetic plays in cervical cancer recurrence since this will provide novel opportunities for treatment options.
The purpose of this study was to evaluate the current developments in the field of epigenetic research on cervical cancer recurrence, including the role these alterations play in the evolution of the illness, their prognostic significance, and their application in targeted therapy.
Keywords: Cervical cancer, Recurrence, DNA methylation, HPV, Epigenetics.

I. INTRODUCTION

Cervical cancer is a major global health concern because of its significant mortality rate [1]. In India, cervical cancer ranks second among all female cancers in terms of fatality ratio. The main cause of the high death rate is that most patients receive a diagnosis at a metastatic stage in addition to a stage III or IV diagnosis. For patients with Federation of Gynecology and Obstetrics (FIGO) stage IB-IIA and IIB-IVA illness, respectively, the recurrence rates for cervical cancer are 11% to 22% and 28% to 64% (2). According to some research, up to 70% of patients with stage III to IVB will experience recurrences (3, 4). Recurrent cervical cancer is still very difficult to treat, and even with intensive therapy, the 5-year overall survival (OS) rate is less than 5%. This is especially true for patients who recur in a field that has previously received radiation therapy (9–11). Numerous factors contribute to the poor prognosis of recurrent cervical cancer, such as the tumour's biological behaviour, the contraindication of repeat radiation therapy in the same field, the tumour's limited response to systemic chemotherapy or targeted therapy, and the uncertainty surrounding the role, indication, and scope of surgical therapy (12, 13). As a result, while choosing a course of treatment, one should consider both the benefits and drawbacks of the chosen course of action as well as any important variables that may affect the prognosis. However, selecting a course of treatment is difficult and highly individualized because of the complicated features of recurrent cervical cancer and the lack of trustworthy information; current guidelines only offer general recommendations [14, 15]. Repetition is often a common cause of impermanence. The American Cancer Society defines cancer recurrence as the reappearance of cancer after a patient has fully recovered from their initial diagnosis. Recurrent cancer is the same disease that was first identified; it may occur in the same part of the body or a different one, but it is still considered to be the same type of cancer. For example, if cervical cancer comes back in the pelvic area, it is still classified as cervical cancer dealing with recurrent cancer can be very challenging, as it tends to be more aggressive than before and there are few treatment options available [16]. Therefore, there is an urgent call for more effective treatment ways. Epigenetic biology has shown great potential over time and can revolutionize treatment options for recurrent cancer. Epigenetic is an emerging field in cancer treatment as well as in the development of biomarkers. Several studies reveal that the development of cancer is planned by epigenetic regulation; these include aberrations in DNA methylation, chromatin-remodelling, post-translational modification of histones, and microRNA processing. Epigenetics gives a new understanding of cancer biology. It also provides advanced insight into the early diagnosis and prognosis of cancer. It would not be an exaggeration to say that epigenetics is a boon for cancer.

II. CERVICAL CANCER

Cervical cancer is one of the most serious and challenging cancers due to its worldwide occurrence. In developing countries, cervical cancer is often the most common cancer in women and may constitute up to 25% of all female cancers. Cervical cancer is preceded only by breast cancer as the most common cause of death from cancer in women worldwide [1]. The second most prominent cancer in India is cervical cancer. Cervical cancer is histopathological classified into two types, as follows:

1) In the cervix, squamous epithelial cells give rise to squamous cell carcinoma.
2) Mucus-producing glandular cells of the endocervix are the origin of adenocarcinoma.
3) Adenosquamous carcinoma and neuroendocrine carcinoma are fewer common forms {17].

A long-term infection with a high-risk oncogenic HPV strain is the main cause of cervical cancer. Papillomaviridae is a family of viruses that includes HPV. Papillomaviruses are common; they have been found in humans and many other species. Each of these viruses is unique to its host. Differences in genomic data have allowed for the classification of HPV into over 200 distinct forms, all of which are currently recognized. Eighty-five HPV genotypes are well characterized among them. A total of 120 isolates have been partially characterized as possible novel genotypes [18].

HPVs are classified as coetaneous or mucosal types, and they can infect basal epithelial cells of the skin or inner lining of tissues. Coetaneous HPV strains affect the hands and feet and are epi-dermitrophic. Different forms of mucosal infection infect the anogenital epithelium, respiratory tract, mouth, or throat. They are divided into two categories based on their correlation with precursor lesions and cervical cancer, as well as the carcinogenic potential of HPV. Primarily "high-risk" HPV and "low-risk" types: 16, 18, 31, 33, 39, 45, 51, 52, 56, 58, 59, 68, 82 Included in high-risk HPV were kinds 6, 11, 40, 42–44, 54, 61, 72, and 81 Low risk.HPV-16 and HPV-18 are the most common types in cervical cancer cases [19]. The HPV virus is a non-enveloped, little virus.

Its eight kilobases of double-stranded circular DNA are split into three sections:

a) The Long Control Region (LCR) acts as a regulator of DNA replication,
b) Early region (E1, E2, E4, E5, E6, and E7) it plays role in viral replication and carcinogenesis,
c) Late regions (L1 and L2) help in viral capsule production [20].

III. EPIGENETIC ALTERATION

A. Responsible Epigenetic tools

The epigenetic mechanism has two main components one is DNA methylation and the second is histone modification. Histone modification has different patterns associated with distinct transcriptional states through interaction flanked by histone readers, writers, and erasers. Six different groups of enzymes help in histone modification, carringing different functions to regulate cells' epigenetics. These groups are DNA methyltransferases (DNMTs), binding methyl CpG binding proteins (MBPs), HDAC (Histone deacetylases), HAT (Histone acetyltransferases) and polycomb-group (PcG) proteins, and microRNAs.

Methylation is the addition of methyl groups into the nitrogen bases like adenine, cytosine, and guanine. The processes of methylation are vital during gene expression, transposable element silencing, genomic imprinting, aging, X-chromosome inactivation, and defense against virus infection. The CpG Island present in the promoter of a gene is around 60% of the total genome of humans. At the CpG island, where the cytosine after the guanine is modified by the methyl group. Modified 5methylcytosine represses the gene expression by inhibiting the binding of methyl-CpG-binding protein 2 and methyl-CpG-binding domain protein (MeCP, MBP) to the transcription factor in the promoter. Transfer of methyl group from S-adenosyl methionine (SAM) to the cytosine is controlled by the enzyme DNA methyltransferase (DNMT). DNMT has three types DNMT1, DNMT2, and DNMT3 according to function [22].

DNMT 1 is an enzyme that is required for maintaining DNA methyl transfer, so it gives the hemi-methylated DNA substrates [21]. DNMT3A and DNMT3B are responsible for de novo methyl transferase activity. DNMT3L plays a role in the methylation of imprinted genes in germ cells. DNMT2 function is not so clear but binding to DNA it may mark specific sequences in the genome [23]. MBP is required for recruiting chromatin remodeling co-repressor complexes on DNA. This family involved methyl–CpG–binding protein 2 (MeCP) and methyl CpG – binding domains 1-4, MBD2, MBD3, and MBD4. tumors-CpG binding domain (MBD) occupancy has a specific profile of gene and tumor type specific. The relation between DNMT and MBD is very crucial in tumorigenesis [24]. HAT is a remodeling enzyme of chromatin, leading to the acetylation of lysine residues of histones 3 and 4 to make active chromatin while the removal of acetylation is carried out by HDAC to make repressive chromatin. In cancer cells, HAT is altered by MOZ-CBP (monocytic leukemia zinc finger protein –CREB binding protein) and global loss of acetylation created by K16-H4. HAT p300/CBP regulates the transcription of many genes.

In cervical cancer, it is associated with acetylation of p53 and HPV E7. HDAC mutation creates sporadic carcinomas as well as more anti proliferative and pro-apoptotic effects of histone deacetylase inhibitors. The association between E7 and HDAC1/2 plays a role in transcriptional regulation to increase the level of E2F2mediated transcription in differentiating cells to arrest S phase [25].

Polycomb group protein (PcG) is a chromatin modifier, it has two groups polycomb repressive complex 1 (PRC1) and polycomb repressive complex 2(PRC2). PRC1 can silence gene expression. PRC2 also silences and reacts to silence chromatin by methylating histone H3lysine 9 and 27. In cervical cancer, PRC2 is found to be highly overexpressed [26].

Epigenetic modifications occur continuously throughout life; however, some variations are accountable for certain diseases. One such disease is cancer; however, a cancer recurrence can be extremely deadly and accelerate the process of dying. Epigenetic modifications have a rapid and significant influence on cancer recurrence and can negate all available therapeutic options. The epigenetic alteration demonstrated here (figure 1) is what causes cervical cancer to recur.

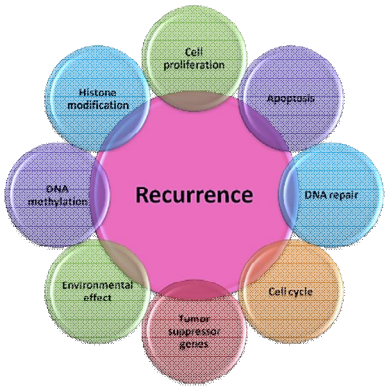

Figure1. Epigenetic changes responsible for cervical cancer recurrence

B. Human Papilloma Virus

Papillomaviridae is a large family of viruses involved in the oncology of the epithelial lining of squamous and mucosal cells. Human papillomavirus (HPV) has 200 different types of variants associated with various infections like warts, STIs (sexually transmitted diseases), anogenital cancer, and oropharyngeal cancers. HPV is mainly found in the basal epithelial cells of the skin (coetaneous) and inner lining of tissue (mucosal) [27].

HPV is an envelope, double-stranded, circular DNA virus with 8kb size. HPV DNA is categorized into three long control regions that take part in DNA replication, the early region plays a major role in carcinogenesis, and the late region produces viral capsid.

The HPV controls viral transcription and replication by the genetic material of the HPV virus, which possesses three functional components that aid in the virus's integration into the host cell, despite its small protein count of just eight to ten.

A function in viral replication and carcinogenesis is played by the Early Region (E1, E2, E4, E5, E6, and E7), while the Late Regions (L1 and L2) aid in the creation of viral capsules. The Long Control Region (LCR) regulates DNA replication.

Viral transcription and replication are controlled by the HPV virus through the careful use of its genetic machinery to coerce host cells. E6 and E7 viral genes are released when LCR interacts with host cell factor E1 and E2 disruption. The virus is carefully using its genetic machinery to coerce host cells. E6 and E7 viral genes are released when LCR interacts with host cell factor E1 and E2 disruption [28].

Transcription of the E6 and E7 genes provides the environment for viral replication by changing the cell growth regulatory pathways and cell cycle excitation. Transcription products deregulate the cell growth factor, cyclin-dependent kinases, and tumor suppressor proteins such as RB1, and p53. The E6 gene product binds to p53 for its degradation through cellular ubiquitin ligase; the main functions of p53 are G1 arrest, cell apoptosis, and DNA repair. E6 is also from a complex with other six cellular proteins whose function is still unknown. To arrest the host cell into the S phase of the cell cycle, the E7 gene binds to the phosphorylated form of pRB by breaking the complex between the pRB and E2F-1. The HPV virus through the E7 gene associated with cyclin E mitotic protein did cellular differentiation and DNA synthesis. HPV required continuous proliferation and delayed differentiation of host cells for that E5 gene to enhance mitogen-activated protein kinase activity [29].

The E2 gene blocks the activity of the E6 and E7 genes as well as keeps the viral replication initiation within the host cell as an extrachromosomal element by binding the E1 gene to the origin of replication located at LCR. The E2 gene mediates the downregulation of the E6 and E7 genes, therefore facilitating the release of p53 and pRB to maintain proper cellular differentiation.

The E4 gene aids in the development and release of viral particles. To activate the capsid gene, the L1 and L2 genes are necessary. A cornified layer of the epithelium is where the HPV virus is discharged after assembling in the nucleus and finishing its virion in the cytoplasm [30].

Based on the portion of the genome that is transferred to the host genome, the HPV virus has two different forms of host integration. The fusion between host DNA and the viral genome is carried out by micro-homology-mediated DNA repair pathways. In the first type of DNA integration, a viral single DNA copy is integrated into the host genome. This type of integration has a very high potential to cause carcinogenesis as compared with the other type. The second type of integration has more viral concatemer into the host genome [31]. The concatemer formed due to the viral DNA replication and recombination in the host genome. Among these concatemer, only a 3'junctional copy is functional and responsible for the carcinogenesis.

The HPV virus-induced carcinogenesis in the host genome is regulated by epigenetic changes, at the 3' site of UTR of the host genome. The oncogenic potential of the virus varies according to the site of integration in the host genome. The HPV is carrying out several epigenetic changes like DNA methylation, histone modification, and post-translational modification into the host genome. These changes lead to the progression of cancer.

C. Cervical Cancer

Epigenetic mechanisms are carried by alien substances like xenobiotics and environmental conditions. Etiology shows that most environmental factors, including geographical regions, stress, nutrition, and toxicants, affect malignant diseases by inducing epigenetic modifications [32]. Other related environmental factors have race, climate, lifestyle, diet, nutritional factors[33], airborne polycyclic aromatic hydrocarbons[34], toxicants (e.g., cocaine), alcohol [35], fungicides or pesticides (e.g., dicofol and vinclozolin)[36],aflatoxin[37], bacteria (e.g., Helicobacter Pylori), viruses (e.g., hepatitis virus[38], heavy metal exposure (e.g., cadmium, arsenic) [39]and endocrine disruptors (e.g., bisphenol-A)[40].

Many studies revealed that nutritional factors play a crucial role in cancer development such as genistein, a phytoestrogen, is known to decrease DNA methyltransferase (DNMT) activity leading to transcriptional activation of RAR-β-2 in cervical cancer [41]. Dietary pattern also influences LINE1 methylation and the risk of developing premalignant lesions [42]. Folate regulates various biological processes like DNA repair and methylation. Diet also influences the probability of HPV persistence [43]. One of the potential factors in the development of high-risk HPV persistence is cervical cell folate concentration and methylation of the DAPK1 and CDH1 genes [44]. Some studies have reported an inverse association between folate level in serum or cervical cells with degree of hypomethylation [45]. Researchers have proven that cur-cumin targets p300/CBP activity in cervical and other cancers [46, 47]. Similarly, genistein is responsible for the effect of histone acetylation or DNA methylation [48, 49]. The other dietary compounds are sulforaphane, genistein, curcumin, resveratrol, and epigallocatechin gallate have shown anticancer activity by targeting epigenetic machinery [50]. Sulforaphane decreases intensity as well as activity of DNMT3B and HDAC1 and DNMTs and HDACs, in HeLa cells [51].

In the development of cervical cancer smoking contributes approximately 2-fold higher risk than nonsmokers [52] which weakens the immune system and induces DNA damage [53, 54]. Cigarette smoking targets DNA methylation levels of many genes, like F2RL3, AHRR, and CYP1A1 [55], these genes target xenobiotic responsive genes and xe-nosensors can affect xenobiotic metabolism and elimination from the body to influence various steps of carcinogenesis. Similarly, researchers show that women who consume alcohol are at higher risk of developing in situ and invasive cervical cancer [56] Alcohol Alcohol-generated metabolites directly or indirectly bind to the transcription factor and change chromatin structure as well as modify gene expression Chronic alcohol consumption can change the hypomethylation status by reducing the SAM levels [57]. The epigenome can be modified by Ethanol metabolism to generate reactive oxygen species. Alcohol intakes modify the level and metabolism of folate in cervical cancer [58]. Study shows that lower folate and vitamin B12 are associated with HPV infection and cervical cancer therefore folate and the one-carbon metabolism pathway are also linked to cervical cancer [59]. The level of DNA methylation is decreased by Hyperhomocysteinemia which can target DNMT 3a and 3b. cigarette smoking has been shown to target DNA methylation levels of many genes, including F2RL3, AHRR, and CYP1A1 [60], suggesting that altered expression of xenobiotic responsive genes and xe-no sensors can affect xenobiotic metabolism and elimination from the body, thereby influencing various steps of carcinogenesis. Tobacco use is associated with tumor suppressor p16 INK4 methylation in squamous cell carcinoma of the cervix and high-grade dysplasia. Also, the expression of mi-RNAs in cervical cancer which can target genes such as EZH2, DNMT3A, ATM, RAC1, p53, and ZEB1 among many others, can influence several tumor-associated phenotypes [61]

The global DNA methylation pattern is altered by aging, which may lead to geriatric-related diseases [62]. Both cancer and its precursor lesions show methylation signatures which are also seen in normal tissues because of aging [63].

The study shows age-related DNA methylation of PCGT in preinvasive cancer lesions also shows [64], an anti-aging and tumor suppressor gene, was silenced in human cervical cancer [65]

It is well known that oral contraceptives increase the risk of female cancers such as breast and cervix. Use of oral contraceptives can transform DNA methylation and monocyte-derived macrophage function. However, the use of oral contraceptives foremost to altered methylation and subsequent cervical carcinogenesis is yet to be proven [66].

Diethylstilbestrol (DES) is a synthetic estrogen, commonly used for treating gonorrhea, atrophic vaginitis, and menopausal symptoms and for postpartum lactation suppression. Aberrant epigenetic modifications and hypermethylation of Homeobox A10 (HOXA-10) are reported to occur upon in-utero exposure to DES [67]. Prenatal exposure to DES is related to clear cell adenocarcinoma of the cervix and vagina. The expression of the EZH2 gene in the mammary gland is increased upon in-utero exposure to DES or bisphenol-A [68]. The over expression of EZH2 is associated with proliferation and progression of cervical cancer and poor prognosis [69]. DES exposure has shown epigenetic and transgenerational effects. It has also altered the expression of DNMT1, DNMT 3A, and DNMT 3B and the transcription factors Sp1 and Sp3 in mice models, suggesting it may alter the DNA methylation and gene expression of transcription factors. The exposure to DES during pregnancy has altered the miRNA expression of oncogenic miRNAs in both fetus and mother [70]. Thus, based on the current study of evidence, DES-induced cervical cancer may be by altering epigenetic modification such as bringing on aberrant DNA methylation. Table 1. Summarizes epigenetic alterations found in cervical cancer.

Table 1. Main epigenetic alterations in cervical cancer

Alteration	Meaning
HPV-related	
Methylation of HPV-E2 binding sites	De-repression of E6 and E7 HPV oncoproteins?
Methylation at HPV-E6 and E7 LCR	Cause or consequence of E6/E7 over-expression?
E6 and/or E7 interaction with DNMTs?	Silencing of cellular tumor suppressor genes?
Interaction between E7 with HDACs	Aid for cell transformation
Interaction between E6 with HATs	Aid for cell transformation
Host cell-related	
Regional DNA hypermethylation	Silencing of tumor suppressor genes
Global DNA hypomethylation	Genomic instability? oncogen over-expression?
Abnormal pattern of chromatin	Unknown
Loss of imprinting at H19/IGF2 loci	Tumor progression?
H3 hyper-phosphorylation & acetylation	Associated with carcinogenesis Progression

D. Affected Cellular Pathways.

Epigenetic mechanisms altering various pathways are cell cycle, DNA repair, apoptosis, hormonal response, tumor cell invasion, and metastasis that are related to oncogenes, inactivated tumor suppressor genes, hormone receptors, cytokine receptors, and growth factor receptors.

1) *Tumor Suppressor Genes:* The epidermal growth factor receptor (EGFR) pathway is responsible for cellular maturation, cell growth, proliferation, apoptosis inhibition, metastasis, and angiogenesis [71]. In processes of cell-cell adhesion E cadherin and H-cadherin (CDH13) play an important role through negative regulation of ligand binding inhibits EGFR [72]. The low gene FHIT level related to increasing the gene p53, results in a poor prognosis altimetry gives higher recurrence of cervical cancer [73]. The mutated gene of Ras and Myc increases the frequency of association with the development of recurrent cervical cancer [74].
2) *Cell Cycle: In* the development of cancer, the cell cycle plays a vital role. The most important pathway in cancer is the phosphatidylinositol 3- kinase (PI3K) pathway which disturbs apoptosis, cellular survival, and proliferation. The PI3K pathway has p53 at its downstream which is tightly regulated by MDM2, p14ARF, p73, MUTL homolog1. The p53 stimulates expression of p21 so arrest cell cycle. The p53 and oncoprotein HPV-E6 together inactivate the cell cycle to deregulate many genes to induce cell proliferation. pRB phosphorylation carried by p21 by inhibiting the activity of CDK2. Cycline dependent kinase inhibitor 1A (CDKN1A) has also regulating p53 which activated by p73 (TAp73) (52). CDKN1A gives protection to

cancer cells from degradation. Cellular immortalization is regulated by p73 through epigenetic deregulation dependent on the production of high-risk HPV E6 and E7 oncoproteins [75]. The study shows that TP73 hypermethylated to a higher extent in Adenocarcinoma and Squamous Cell Carcinoma [76].

3) *DNA Repair:* Cell cycle deregulation is carried out by the p53 and p73 proteins to stimulate the expression of DNA mismatch repair protein Mlh1 or MutL protein homolog 1 (MLH1) protein. MLH1 protein is involved in the intracellular process of recognizing and repairing foreign DNA through the processes of DNA mismatch repair. Hypermethylation of MLH1 increases the susceptibility to cancer by increasing the level of microsatellite instability that is reported in low-risk HPV infection. The advanced recurrence is associated with reduced levels of MLH1 and Fragile histidine triad (FHIT) together with increased p53 levels in cervical cancer [77].
4) *Apoptosis:* The main fisher of a cancer cell is the modulation of apoptosis differently either viruses' oncogenes mediated proliferation, immortalization, and transformation of the normal cell or by breaking signaling aided of the cell to target ubiquitin-proteasome pathway. Virus E6 protein binds to p53 with the E6AP complex and prevents p53 from inducing apoptosis. In this way, physiological apoptotic pathways are disturbed leading to uncontrolled cell proliferation. The transcriptional activity of E2F1/DP1 encourages the proliferation of cells via the S phase that is stimulated by the negative regulator of p53 and pRB. Telomerase reverse transcriptase (TERT) activation through AKT and E2F is responsible for phosphorylation. HPVE6 binds to the TERT promoter to enhance its potential at a significantly higher level that offers telomere elongation and upregulation of vascular endothelial growth factor (VEGF) to contribute to tumor angiogenesis [78]
5) *Cell Proliferation :* Cell proliferation mainly depends on the Wnt signaling pathway. It has a large family of secreted growth factors which are responsible for controlling cell fate, proliferation, migration, tissue architecture, and organogenesis. An important role of Wnt signaling in adult organisms regulates the homeostasis of hematopoiesis, angiogenesis, and adipogenesis. The cell proliferation by Beta-catenin activation is mediated through the binding of E-cadherin. The Wnt signaling pathway has Frizzled family (Fzd) receptors and co-receptors like low-density lipoprotein receptor-related proteins-5/6 (LRP). Cervical cancer cases show the negative regulator of the wnt pathway such as CDH1 and wnt inhibitory factor 1(WIF1), adenomatous polyposis coli (APC). The hypermethylation of WIF1 correlated to a low level of WIF protein which prevents the wnt signaling. The hypermethylation of APC reduces the level of APC in the cytoplasm of cervical cancer cell and significantly increases the level of beta-catenin in the nucleus and cytoplasm, suggesting increasing Wnt pathway [79].

IV. TREATMENT APPROACH FOR CANCER AS WELL AS RECURRENCE

Cervical cancer treatment depends on several factors, including cancer type, stage of cancer, side effects of the drug, and overall health of women. The treatment given to the patient is according to the FIGO and TNM. Cervical cancer has the following steps in treatment according to the infection of the cervix.

A. Surgical treatment
B. Radiation treatment
C. Therapies using medication:

The following kinds of systemic treatments are used to treat cervical cancer: immunotherapy, targeted therapy, and chemotherapy.

1) *Surgical Treatment:* All that surgery entails is the excision of the tumor along with some healthy surrounding tissue from the cervix. The technique of tumor removal is chosen based on its growth. Conization is a technique used to treat cervical cancer. It involves a cone biopsy to remove any abnormal tissue, often known as micro-invasive carcinoma, that can only be seen under a microscope. LEEP is another technique used to remove microinvasive malignancy. The LEEP procedure involves passing an electrical current via a small wire hook to remove tumor tissue. Large size of tumors occupy the organs and then the organ has to be removed with the help of a hysterectomy. A hysterectomy is the process of removal of the uterus and cervix. It has two types one is simple hysterectomy which removes the uterus and cervix second is radial hysterectomy which removes the uterus, cervix, upper vagina, and the tissue around the cervix. The radial hysterectomy also removed an extensive pelvic lymph node. This can be done by using a large cut in the abdomen, called laparotomy, or smaller cuts called laparoscopy. In hysterectomy can remove both the fallopian tubes and both the ovaries is called bilateral salpingo-oophorectomy. The alternative option for hysterectomy is radial trachelectomy, in which this cervix is removed but the uterus is left intact. This process is significant for young patients who want their fertility [80].

2) *Radiation Therapy:* Radiation therapy is the use of X-ray radiation and other radiation to remove tumors. Based on the incidence of radiation site it is two types, external-beam radiation therapy, in which radiation is given from a machine outside the body. Internal radiation therapy or brachytherapy, in this radiation treatment, is given using implants [81].
3) *Therapies using Medication:* Under this type of therapy, different methods are used Chemotherapy, Targeted therapy, and Immunotherapy. Chemotherapy is a drug therapy that is used for the destruction of cancer cells to reduce the growth and proliferation of cancer cells. Targeted therapy uses targets of the cancer-specific genes, proteins, and the epigenetics of cancer growth and survival. The benefit of targeted therapies is they only harm the target limiting damage to healthy cells. Immunotherapy is therapy of the immune system, also called biological therapy, and is designed to such to boost natural defenses to fight cancer within the body. Applying all these therapies is according to the severity of the disease and norms of the FIGO and TNM. The combination of therapy is used during treatment for better results. The combination is like

a) *Neoadjuvant Chemotherapy to Surgery:* In this, the chemotherapy with the radical surgery is applied. It increases the 14% survival rate to using only RT. The main focus of using neoadjuvant chemotherapy (NACT) is primary tumor size reduction, allowing operability; micro metastatic disease eradication; tumor vascularization potential increase, and hypoxic cell reduction [81].
b) *Neoadjuvant Chemotherapy and Radiotherapy:* The treatment concept is chemotherapy before RT (neoadjuvant or induction chemotherapy). The rate of survival increased by 7% in 5 years as compared to the single therapy alone[81].

V. RECURRENCE

The bulk of the care for recurrent cervical cancer is dependent on the place and degree of the recurrence, as well as previous treatment. Approximately 70% of patients receive pelvic radiation therapy at some time during their care, and a poor prognosis is typically linked to a tumor failure in the pelvis that has received radiation. Recurrences of cervical cancer can be classified as extra-pelvic, lateral, or central pelvic .

After initial radiation treatment from the cervix and vagina, or from the vaginal cuff and central scar following radical hysterectomy, central pelvic recurrence typically occurs. This relapse is restricted to the vaginal vault, yet it might also affect the bladder or rectum more often.

Diseases on the parietal and visceral pelvic sides were involved in lateral pelvic recurrence. The second comes from the paracervix or scars from the paracervical excision; that is, the obturator nerve below the site of the earlier pelvic lymph node metastases, which are often positioned above the level of the obturator nerve. The most common sites of extra-pelvic metastases are the liver, lungs, para-aortic lymph nodes, and bone [82]. Pelvic recurrence on the side of the center: In patients with a pelvic recurrence, radiation therapy or concurrent cisplatin-based chemo-radiation therapy are the primary forms of treatment following radial hysterectomy alone [82] But compared to primary radiotherapy, the level of difficulty in safely delivering high doses of radiation is higher in this clinical scenario because the only available treatment option, brachytherapy, is restricted to treating the vaginal vault alone, and the radiation dose to the bowel rises because of the presence of post-surgical adhesions. Intensity-modulated radiotherapy (ImRT), a crucial new treatment, enables the administration of varied radiation doses to a specific target volume. Researchers found that combining IMR with chemotherapy is a very acceptable way to achieve improved control of cervical cancer that is progressed or recurring [83].17 In patients with central pelvic recurrence who have had initial radiation for this type of instance, radical hysterectomy is the course of treatment. However, depending on the difficulties, the survival rate in such cases is poor, ranging from 27% to 72%. [75–80] Tumour size at the time of a radical hysterectomy is highly connected with the clinical prognosis; almost 90% of women with <2 cm lesions survive 5 years actuarial, whereas 64% of women with bigger lesions ($p<0.01$) have a 5-year actuarial survival. Hence, radical hysterectomy is significant only in highly selected cases of recurrence those have small recurrent lesions limited to the cervix. A single therapeutic approach for Pelvic exenteration is a medicinal target for patients who have central pelvic failure and are already treated with irradiation. The pelvic exenteration has an original classification into three groups, i.e., anterior, posterior, and total, addressing only the nature of the pelvic viscera removed. The new subclassification according to Magrina [84] and Chiva [85] into type I (supra-levator), type II (infra levator), and type III (with vulvectomy), which takes the levator ani muscle as a reference point and which offers a better definition of the extent of resection and the anatomical changes associated with each operation. Distant recurrence or loco-regional recurrence:- it is an advanced stage of recurrence that amenable to surgery or radiotherapy the role of chemotherapy in this clinical setting is only palliative. Chemotherapy administration is exaggerated by several factors, such as limited drug distribution in previously irradiated tissues, renal dysfunction due to ureteral obstruction, and decreased bone marrow function due to prior irradiation. The most widely used drug is cisplatin which has a response rate of 17-38% with a median overall survival of 6.1-7.1 months [86].

Rather than using cisplatin monotherapy, Cisplatin-based doublets with topotecan or paclitaxel have demonstrated superiority in terms of response rate and PFS. Cisplatin combination with topotecan showed superior rate of survival compared to cisplatin alone. Both trials also demonstrated that the response rate was inferior in patients previously exposed to CRT. The three-drug combination of paclitaxel–ifosfamide–cisplatin(TIP) has hopeful responses with an overall response rate of 62%, with a complete response of 26%[86]. It is considered an active treatment with satisfactory toxicity in advanced/relapsed cervical cancer. Whereas four different cisplatin-based doublets with paclitaxel, topotecan, gemcitabine, or vinorelbine were unable to prove superiority in a large randomized phase III trial [87].

The preferred first-line treatment in case metastatic or recurrent cervical cancer is Paclitaxel and cisplatin combined with bevacizumab based on the balance between efficiency and toxicity profile [I, A] In patients succeeding following first-line therapy, different cytostatic agents, including vinorelbine, topotecan, gemcitabine or nanoparticle albumin-bound paclitaxel have been evaluated. However, response rates are low, and the duration of responses is short. Therefore, no recommendation can be given about the most effective second-line treatment. RT can play an important role in patients with recurrent disease, in the case of oligometastatic disease, and for patients with only nodal metastasis in the pelvic, periaortic, and/or supraclavicular regions, as high-dose RT often leads to long-term disease control and a prolonged progression-free interval. Short-course palliative RT is used to treat symptoms from distant metastases[81].

VI. CLINICAL APPLICATION OF EPIGENETICS

A. Early Detection Marker

Early detection markers are essential to detect the disease before the time of development. In the case of cervical cancer for decades the PAP smear has been used as an early detection marker. The epigenetic marker opens a new window of biomarkers to detect the disease before starting the symptom. Epigenetic targets present at each stage of cancer that are used for early detection or as prognostic markers. A prognostic marker can be defined as the marker which predicts an outcome in the lack of therapy or it predicts an outcome from that of patients without the marker, despite empiric therapy [26].

Table 2. Epigenetic markers and their clinical prediction

Epigenetic marker	Tissue source	Clinical prediction
CpG Methylation related		
CCNA1	Tumor	Distinguish CIN2 from CIN3,early diagnosis of invasive cancer
P16INK4A	Tumor	Low-grade dysplasia
PTEN	Tumor	Early events in the development of cervical cancer
DAPK	Plasma	CINII/high-grade precancerous lesions
RASSF1A	Tumor	Early diagnosis of cervical intraepithelial neoplasia (CIN)
MGMT	Tumor	Cervical oncogenesis progression
CADM1 and T-lymphocyte maturation-associated protein (MAL)	Tumor	Degree and duration of cervical disease
CDH1 and CDH3	Tumor or serum	Early detection/invasive cancer[76]

B. Tumor Progression Detection Marker

The rate of cell proliferation in a tumor is generally thought to be of prognostic importance, and until recently the only means available to the pathologist to assess this was to count the number of mitotic figures, a technique fraught with difficulties and pitfalls. The two proliferation antigens that have been most widely studied are proliferating cell nuclear antigen (PCNA), which is expressed during the G1 and early S phases of the proliferative cycle, and Ki-67, which is expressed during the G2 and mitotic phases of the cycle. Ki-67 is the more reliable indicator of the growth fraction of a tumor, largely because PCNA has a long half-life and may still be demonstrable in post-mitotic cells.PCNA is a proliferation marker but has limitations multiple factors affect staining intensity Ki67 is a proliferation marker but limited multiple factors affect expression levels[88.]

C. Epigenetic Therapies

Epigenetic alteration, suggests strategies to revert the epigenetic changes via pharmacological manipulation. Currently, two main classes of epigenetic drugs, methylation inhibitors, and HDAC inhibitors, are in clinical trials for the treatment of cancer. 5-Azacytidine and 5-aza-2′-deoxycytidine are DNA methylation inhibitors that have shown their clinical activity against hematological neoplasms. However, they display poor activity against solid tumors, and their severe toxic side effects restrict their use in clinics. Hydralazine, a peripheral vasodilator drug is a well-tolerated and stable DNA methylation inhibitor. It can induce demethylation of promoter sequences and reactivation of the mRNA transcription and protein synthesis of particular tumor suppressor genes with minimal toxicity. Another cardiovascular drug, procainamide, has also shown its potential to re-express silenced gene with functional protein. Trichosanthin (TCS), a bioactive component isolated from a Chinese medicinal herb has been shown to have the capacity to restore the expression of methylation-silenced tumor suppressor genes [88].

VII. PROSPECTS FOR THE EPIGENETIC FIELD IN RECURRENCE IN THE FUTURE

Gynecologic oncologists face a challenging case when recurrent cervical cancer occurs. Concurrent cisplatin-based chemo-radiation can be used to treat patients who have central or lateral pelvic failure following surgery alone. For women who have central pelvic recurrence following irradiation, pelvic exenteration typically represents the only treatment option with a curative objective. The preferred treatment for isolated para-aortic lymph node recurrence is concurrent cisplatin-based chemo-radiation, which has a good prognosis in asymptomatic individuals. Patients who have remote or loco-regional failures and are not responsive to surgery or radiation therapy are given chemotherapy to provide palliative care. When compared to single-agent cisplatin, combination chemotherapy based on cisplatin boosts response rates; nonetheless, the median overall survival is often less than a year. However, some cases of unexpected long-term disease-free survival after salvage chemotherapy have been reported in the literature. It is now well established that epigenetic aberrations can regulate the expression of oncogenes or repression of tumor suppressor genes which make this alteration a powerful line for investigation of cancer pathogenesis and progression. For cervical cancer, we can highlight several genes that undergo epigenetic alteration at the level of DNA methylation, histone modification, or noncoding RNA action. Analysis of these alterations and information about them can be a reliable screening method for women at high risk for this disease and can establish and date biomarkers for the detection of the disease.

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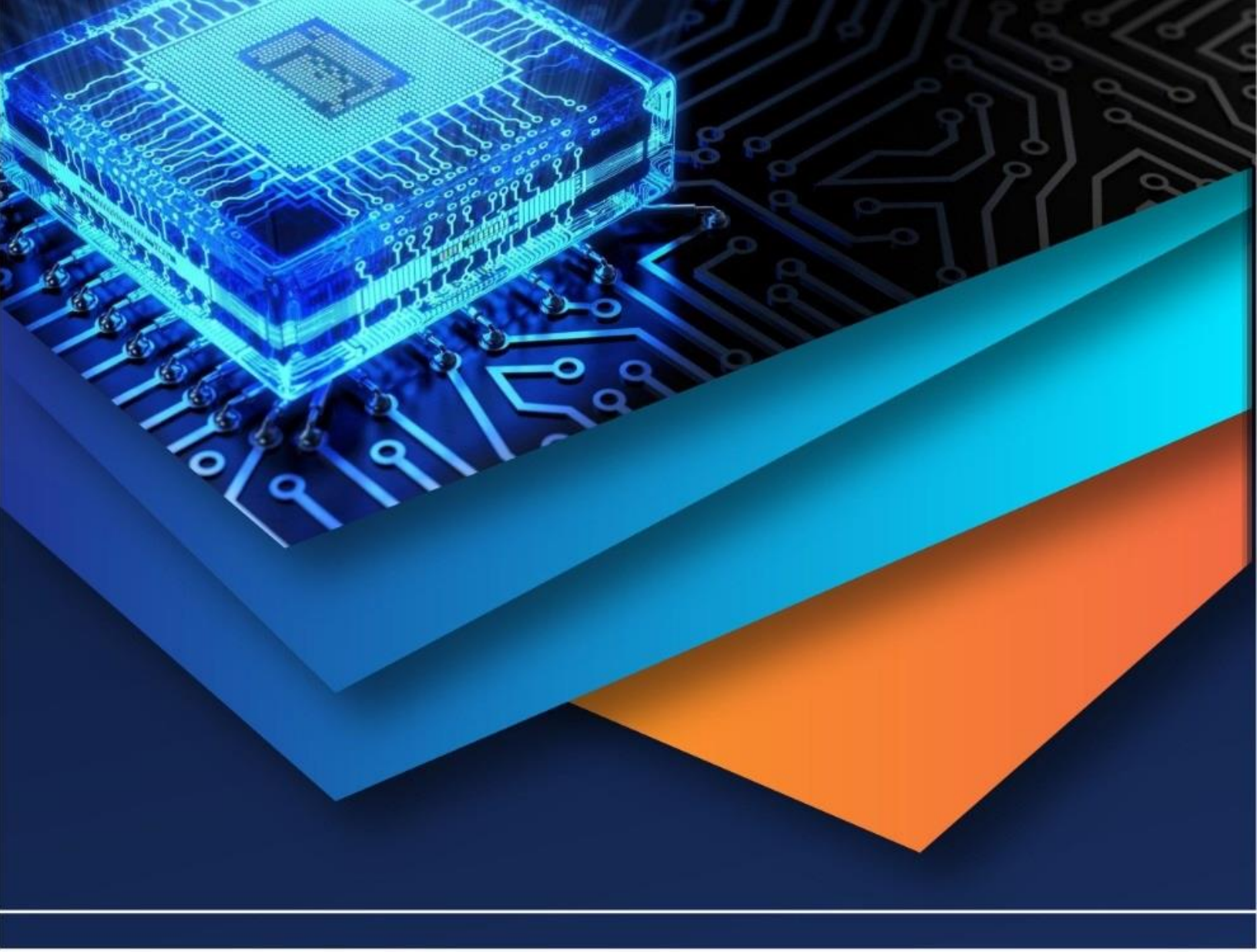

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