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"An Overview of Cervical Cancer Pathophysiology, Screening and Its Management"

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ABSTRACT: Cervical cancer is a major gynaecological cancer which involves uncontrolled cell division and tissue invasiveness of the female uterine cervix. With the availability of new technologies researchers have increased their efforts to develop new methods for early diagnosis, and evaluation and monitoring of therapeutic treatments. This approach will help in the development of early diagnosis and in increasing treatment efficacy with decreased recurrence. The present review gives overview of early diagnosis, pathophysiology and Management of cervical cancer.

KEYWORDS: Cervical cancer; hr-HPV; TCT; Vaccine; Biomarkers; Diagnosis; Prognosis; human papillomavirus; cervical neoplasia; Cancer antigen; Magnetic resonance imaging.

I. INTRODUCTION

Cancer is characterized by abnormal, uncontrolled cell proliferation due to genetic and epigenetic changes that regulate cell growth, differentiation and cell death [1]. Cervical cancer, originating in the cervix, is predominantly caused by prolonged infections of high-risk HPV types[2].

Cervical carcinogenesis is primarily driven by human papillomavirus (HPV), a sexually transmitted virus with over 200 genotypes[3]. Among these persistent infection with high-risk HPV types such as HPV-16 and HPV-18 poses the greatest risk for the development of cervical precancerous lesions and invasive cancer[4].

Cervical cancer is a highly preventable disease with declining incidence because of effective screening and vaccination to prevent the most carcinogenic strains of HPV[5]. Key prevention initiatives include completing the recommended vaccination series, standardized screening, and education about contributing factors to encourage avoidance of associated risks. Condom use is reported as approximately 70% effective in reducing the transmission of HPV[6].

II. THE EPIDEMOLOGY OF CERVICAL CANCER

- The World Health Organization (WHO) reported that, cervical cancer comprises 12% of all cancers globally and it is the most common gynaecological malignancy in the world[6].
- The burden of cervical cancer in India is enormous, accounting for about 20% of all cancer-related deaths in women and it is the main cause of death in middle aged Indian Women[7].
- Persistent HPV infection causes more than 99% of all cervical cancers. Every year, there are more than 500,000 new cases of cervical cancer and approximately 250,000 deaths due to cervical cancer worldwide. Eighty percent of cases occur in developing countries[8].
- According to the World Health Organization (WHO), cervical cancer will cause more than 443,000 global deaths annually by 2030.
- The mortality rates of cervical cancer vary based on population locations and economic conditions. Approximately 85% of the deaths occur in underdeveloped or developing countries[5].

III. ETIOLOGY

- HPV is transmitted by skin-to-skin contact, including during sexual intercourse, hand-to-genital contact, and oral sex[8].
- Risk factors for HPV and cervical cancer include young age at sexual initiation, multiple sexual partners, high parity, smoking, herpes simplex, HIV, coinfection with other genital infections, and oral contraceptive use[9].

IV. SIGNS AND SYMPTOMS OF CERVICAL CANCER.

Detecting cervical cancer can be challenging as it. Often shows no early signs. Symptoms typically manifest only after the cancer has begun to spread,

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However, some indicators of early-stage cervical cancer include:

- Vaginal bleeding after intercourse
- Vaginal bleeding after menopause
- Irregular vaginal bleeding between periods, along with heavier or longer-than- usual menstrual cycles
- Pelvic discomfort or pain during sexual intercourse[10].

V. PATHOPHYSIOLOGY.

5.1Human papillomavirus

The development and progression of cervical cancer are significantly influenced by dysregulation ion of the cervical microbiota by **human papillomavirus (HPV),** modulation of the immune response, and the emergence of new mutations causing genomic instability [11].
The progression of high-grade lesions and cancer is seen in the presence of other carcinogenic risk factors.

5.2Within HPV DNA, the incorporations E6 and E7 interfere with the critical host cell cycle; specifically, E6 interferes with suppressive tumour protein p53, whereas E7 interferes with retinoblastoma protein (pRB). Additionally, the E5 protein may play a role in immune evasion. These are significant factors in HPV-related neoplasia, including primary vagina cancer [12].

- Additionally, viral infections such as Epstein-Barr virus, Hepatitis B and C viruses, and human herpesvirus contribute to cervical cancer by interfering with cellular regulatory proteins, Inactivating tumor suppressor genes, evading host immune responses, inducing persistent inflammatory responses, triggering epigenetic modifications, stimulating angiogenesis, and activating telomerase. Dysregulation of genes like cyclin-dependent kinase inhibitor ZA (CDKN2A), SRY-box 17 (SOX17), and checkpoint kinase 1 (CHEKI) further promotes cancer cell growth by disrupting DNA repair mechanisms and apoptosis due to HPV genome integration into host chromosomes and inactivation of tumor suppressor proteins is 153 153 and retinoblastoma (pRb)[11].
- Oxidative stress and microRNAs are believed to play a role in cervical carcinogenesis [11]
- Prognostic factors for cervical cancer include the number of retrieved lymph nodes, age at symptom onset, use of a uterine manipulator during laparoscopic surgery, and the combination of retrieved lymph node count and FIGO staging system. Patients with a higher number of retrieved lymph nodes experience significantly better progression-free survival (PFS). Younger patients (aged 25 to 39) at symptom onset have a poorer prognosis, whereas laparoscopic therapy using a uterine manipulator is associated with a better prognosis. Combining the retrieved lymph node count with the FIGO staging method enhances the prediction of PFS, serving as potential predictors of Cervical cancer prognosis [13].

VI. SCREENING OF CERVICAL CANCER.

Most cervical cancer is asymptomatic and will not present with an overt mass in the early stages. Diagnosis may require further evaluation of symptoms and testing to determine whether the disease is cervical cancer. A diagnostic biopsy is needed to finalize the diagnosis. Rarely a routine Pap smear may identify metastatic cancer on the uterine cervix [14].

Cervical cancer may be suspected on analysis of a Pap smear or visualisation of a lesion on the cervix. A biopsy sample must be taken from any suspicious lesion, because many Pap smears are non-diagnostic or falsely negative in the presence of invasive cancer. If a biopsy sample shows cells suggesting microinvasion, and if the patient does not have a grossly apparent invasive cancer, a cone biopsy should be done. For accurate staging of clinically occult lesions, sufficient underlying stroma must be obtained to allow for adequate assessment of the depth and width of invasion below the basement membrane.
[15,16].

6.1 STAGING AND PROGNOSIS.

Once a tissue diagnosis of invasive carcinoma has been established, the patient is staged. The Stage is determined at the time of primary diagnosis and should never be changed, even after recurrence or on discovery of more extensive disease during surgery. Stage is determined clinically, on the basis mainly of the size of the tumour in the cervix or its extension into the pelvis. Modifications to the FIGO staging system were made in 1994 to clarify the description of microinvasive cervical cancer (stage IA1 and IA2) and to subdivide stage IB into IB1 (tumour<4 cm) and IB2 (tumour>4 cm) tumours.

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TABLE:1 FIGO STAGING FOR CERVICAL CANCER

STAGES	DESCRIPTION
➢ **Stage 0**	Carcinoma-in-situ, intraepithelial carcinoma
➢ **Stage I**	
• Stage IA	Invasive carcinoma strictly confined to cervix
• Stage IA1	Invasive carcinoma identified microscopically (all gross lesions, even with superficial invasion, should be assigned Measured invasion of stroma 3-0 mm or less in depth and no wider than 7-
• Stage IA2	0 mm
➢ **Stage IB**	Measured invasion of stroma more than 3-0 mm but no greater than 5-0 mm in depth and no wider than 7-0 mm.
• Stage IB1	Preclinical lesions greater than stage IA or clinical lesions confined to cervix Clinical lesions of 4-0 cm or less in size
• Stage IB2	Clinical lesions more than 4-0 cm in size
➢ **Stage II**	Carcinoma extending beyond cervix but not to pelvic sidewall; carcinoma involves vagina but not its lower third Involvement of upper two-thirds of vagina, no parametrial movement.
• Stage IIA	Obvious parametrial involvement
• Stage IIB	
➢ **Stage III**	
• Stage IIIA	Carcinoma extending onto pelvic wall; on rectal examination, there is no cancer-free space between. tumour and pelvic sidewall. The tumour involves lower third of the vagina. All patients with parametrial involvement hydronephrosis or non-functioning kidney are included unless known to be the result of other causes.
• Stage IIIB	Involvement of lower third of the vagina; no extension to pelvic sidewall Extension to pelvic sidewall and/or hydronephrosis
➢ **Stage IV**	
• Stage IVA	Carcinoma extends beyond true pelvis or clinically involves mucosa of bladder or rectum. Bullous oedema does not allow a case to be designated as stage IV. Spread of growth to adjacent organs
• Stage IVB	Stage IVB Spread to distant organs

Currently, the common screening methods include cytological examination, HPV detection, ultrasound examination, magnetic resonance examination[17,18].

6.2 Cytological examination.

Cervical cytology is the simplest and most effective examination method for early diagnosis of cervical cancer. This technique plays an important role in diagnosing malignant tumours and precancerous lesions [19].

6.3 HR-HPV detection.

In recent years, HPV detection has become the necessary screening method for cervical cancer. HPV testing identifies women with cervical diseases and those at risk of developing cervical cancer later. HPV detection provides detailed information on HPV genotyping, which helps clinicians understand the related pathology and possibly provides more precise treatments [19].

6.4 Biomarkers of cervical cancer.

A biomarker is a characteristic that can objectively be measured as an indicator of normal pathogenic processes or a pharmacological response to a therapeutic intervention[20].

The primary goal of biomarker development is not only focused on upgraded therapeutics but also focused on improved methods to deter-mine an individual's risk assessment in cancer development, and to detect cancers at early

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stages, when they can be more effectively treated Cancer[21].

VII. PREVENTION OF CERVICAL CANCER

Hippocrates said, "Prevention is better than cure," which is particularly true for cervical cancer[22].

Three prophylactic HPV vaccines. Were approved in the 2000s capable of preventing infection with multiple HPV types known to cause cervical cancer. These are the bivalent vaccine Cervix, the quadrivalent vaccine Gardasil, and the 9-valent vaccine Gardasil9. Cervix targets high-risk HPV16/18 that are responsible for 70% of cervical cancer cases, Gardasil prevents infection of HPV16/18/6/11, and Gardasil9 covers HPV31, 33, 45, 52, and 58 in addition. The guidelines for HPV vaccination are slightly different for eligibility in different countries. The WHO suggests that the most optimal vaccination population is girls aged 9 to 13 without sexual experience. The American Cancer Society recommends that the best age to receive the vac- cine is 11 to 12 years[23].

TREATMENT OF CERVICAL CANCER

Table-2 Treatment algorithm of cervical cancer[24,25]

Stage	Clinical features	Treatment
➢ **IA1**	Invasion 3·0 mm or less With lymphovascular space invasion	If patient desires fertility, conisation of cervix If she does not, simple hysterectomy (abdominal or vaginal)
		Hysterectomy with or without pelvic lymphadenectomy
➢ **1A2**	3-0-5-0 mm invasion, <7-0 mm lateral spread	Radical hysterectomy with pelvic lymphadenectomy Radiotherapy
➢ **1B1**	Tumour 4 cm or less	Radical hysterectomy with pelvic lymphadenectomy plus chemoradiotherapy for poor prognostic surgical-pathological factors Radiotherapy
➢ **IB2**	Tumour bigger than 4 cm	Radical hysterectomy with pelvic lymphadenectomy plus chemoradiotherapy for poor prognostic surgical and pathological factors Radiotherapy
➢ **IIA**	Upper-two-thirds vaginal involvement	Radical hysterectomy with pelvic lymphadenectomy Chemoradiotherapy
➢ **IIB**	With parametrial extension	Chemoradiotherapy
➢ **IIIA**	Lower third vaginal involvement	Chemoradiotherapy
➢ **IVA**	Local extension within pelvis	Chemoradiotherapy
➢ **IVB**	Distant metastases	Primary pelvic exenteration Palliative chemotherapy

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		Chemoradiotherapy

Table-3 CURRENT THERAPETIC DRUGS.

Name	Mechanism of action	Pros or cons
➢ **Cisplatin**	Bind with genomic DNA (gDNA) or mitochondrial DNA (mtDNA) to create DNA lesions, block the production of DNA, mRNA and proteins, arrest DNA replication, and activate several transduction pathways of necrosis or apoptosis.	Gold standard for treating cancer; drug resistance[26].
➢ **Carboplatin**		Carboplatin is less nephrotoxic, neurotoxic and ototoxic, and much less emetogenic than Cisplatin[27].
➢ **Paclitexel**	Paclitexel induces mitotic arrest and apoptosis through stabilization of the mitotic spindle. This inability deconstructs the mitotic spindle during mitosis leads to the cessation of the cell cycle with the arrest at the G2/M phase	Lack of aqueous solubility; as an potent radiosensitizer that causes cell cycle arrested at the G2/M phase[28].
➢ **Fluorouracil**	Working as an antimetabolite to prevent cell proliferation, it primarily inhibits the enzyme thymidylate synthase to block the thymidine formation required for DNA synthesis	Along with a long-term side effect: cognitive impairment[29].
➢ **Topotecan**	Topotecan is a semisynthetic analog of camptothecin (topoisomerase I inhibitor), which inhibits the topoisomerase I enzyme, causes doublestranded DNA breaks during replication, and leads to cell death.	Combination with and/or cisplatin radiationtherapy, high produces objectiveresponse rates and prolongs survival[30].

VIII. CONCLUSION

With the development of cervical cancer screening ,prevention and its management the morbidity and mortality of cervical cancer have declined in recent years. Primary HPV detection is becoming more popular, replacing other screening methods in developed and developing countries. In the meantime, applying the prophylactic vaccines greatly reduces cervical cancer occurrence and certain types of HPV infection

More efforts should be focused on molecular mechanisms underlying how HPV triggers cervical cancer information. In summary, the combination of next-generation screening and prevention and management approaches will contribute to the goal of "the global elimination of cervical cancer."

ABBREVATIONS

HPV, human papillomavirus; hr-HPV, high-risk HPV; WHO, World Health organization,

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