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Cervical Cancer: An Overview

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Abstract: *Viral infections play a key role in causing many of the human cancers (i.e., 15-20%). Infections caused by these kinds of oncogenic viruses can initiate different stages of carcinoma. One such oncogenic virus is the Human Papilloma Virus (HPV), among the different strains of which around 15 strains are related to the cause of cervical cancer. Despite having effective screening and diagnostic methods, cervical cancer continues to be of major concern worldwide. A wide range of differences in cervical cancer prevalence does exist from one geographic region to another. Many studies have been conducted globally on the prevalence and epidemiology of HPV infection and the cancer causing properties of different HPV genotypes. However, there are still many countries where the population based prevalence has not yet been identified. A number of techniques for accurate and cost-effective screening of cervical pre-cancerous lesions exist, along with the availability of different vaccines showing coverage towards different sets of high-risk HPV genotypes. Yet, around 80-90% of the HPV infection occurs in low income countries that lack effective screening and vaccination programmes. In developed countries, HPV infections have decreased more than half over a period of time by introducing screening and vaccination programmes. Screening high-risk populations for HPV infections can drastically reduce the risk of women dying from cervical cancer. Multiple modalities exist for the complete eradication of precancerous as well as malignant lesions, including surgical, radiation and chemotherapy. The advent of screen-and-treat method over that of screen, diagnosis and treat modality has hastened the process of cervical cancer treatment. The aim of this review was to provide an update regarding various factors that cause cervical cancer, screening methods, vaccination programme, and the existing treatment option to treat cervical cancer.*

Keywords: *Cervical cancer, cervix, ectocervix, endocervix, precancer, cervical intraepithelial neoplasm (CIN), invasive cervical cancer, Human Papillomavirus (HPV)*

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I. Introduction

Cancers are a group of cell-cycle dysregulation disorders that can originate in any type of cell, tissue or organ, and can also spread, or metastasise, to other adjacent or distant tissues. Cancer has the second highest contribution towards global mortality, accounting for about 96 lakh deaths in the year 2018, making it one of the most unnerving diseases in the world[1]. Cervical cancer is the 4th most common cancer among females, which occurs in the cervix of the uterus[2]. It can emerge as squamous cell carcinoma, which involves the squamous epithelial lining of the ectocervix and accounts for about 80% of the cervical cancers, or adenocarcinoma, which is the neoplasm of the mucus-secreting glandular cells of the endocervix and accounts for about 20% of the cervical cancers. The disease is often asymptomatic at early stages, with non-specific symptoms of intermittent or post-menopausal, menstrual flow, increased foul-smelling vaginal discharge, and non-menstrual pelvic pain[3]. Despite the availability of multiple screening and diagnostic techniques as well as various treatment modalities, cervical cancer still remains one of the leading causes of deaths in females in India, owing to the community-based barriers for screening the susceptible population. In addition to the existing barriers, the growing population size makes it even more challenging to screen all of them effectively, resulting in an increased number of women being diagnosed with cervical cancer in the advanced stages, particularly the low-income population who lack knowledge and cannot afford the expensive diagnostic procedures. Although it is a well established fact that Human Papilloma Virus (HPV) is the most common causative agent of this malignancy, multiple aspects with this regard are still left untouched, along with the existence of various outcome-based conspiracies with respect to vaccination. This article gives a wider insight of the incidence, HPV as a causative agent, diagnosis and staging of the cancer along with treatment modalities for the disease and HPV vaccination,

focussing on the advances and challenges related to each of them.

II. Epidemiology

Cervical cancer accounts for over 6.6% of all cancers in women, of which over 54.7% women fail to survive. In the year 2018, about 5.7 Lakh women were diagnosed with cervical cancer around the world, with over 3 Lakh deaths being recorded. The highest incidences were recorded in Eastern and Southern Asia, Eastern Africa, South America and Southern and Central Europe. Indian women constitute more than 17% of the global cervical cancer reports and over 19% of the annual deaths occurring due to the malignancy. India witnessed the highest number of cervical cancer cases in 2018, with about 1 lakh women being diagnosed with the disease and more than 60 thousand of them dying due to it. Women between the age of 20-60 years are more susceptible, and account for approximately 70% of the total annual incidence of cervical cancer, followed by women over 60 years of age and a negligible number of girls below the age of 20 years[4]. Around 85% of the global deaths due to cervical cancer have been recorded in underdeveloped as well as developing countries, with approximately 18 times higher death rate in low-income and middle-income countries in comparison to wealthier countries. Although about 95% of the malignant lesions are found to be due to infection by Human Papillomavirus (HPV), various other contributing factors, such as tobacco smoking, previous history or presence of chlamydia infection, consumption of diet with less fruits and vegetables, sexual intercourse or first full-term pregnancy below the age of 17 years, prolonged use of hormone replacement therapy for contraception, increased parity and existing Human Immunodeficiency Virus (HIV) infection[5-7].

III. Gross Anatomy And Microscopy Of The Cervix

Cervix is the part of the female reproductive organ that connects the body of the uterus to the vagina. It is guarded by 2 orifices, the external orifice which opens into the vagina, and the internal orifice, which extends into the uterus. The epithelial lining surrounding the external orifice is termed as ectocervix, which constitutes of stratified non-keratinised glycogen-rich squamous epithelium and is visible conspicuously as a pale-pink region in per-speculum examination, while that located above the external orifice is called as endocervix, which constitutes of a single layer of glandular mucus-secreting columnar cells that appears grainy and notably reddish, owing to the underlying highly-perfused stroma which imparts its colour to the single-layered endocervix. The basal cells of the stratified squamous epithelium of ectocervix are the stem cells that proliferate, migrate and differentiate to form the parabasal, intermediate and superficial layers, where the nucleus and cytoplasm ratio decreases in the same order. The columnar cells of the endocervix exhibit numerous invaginations into the stroma, referred to as endocervical crypts or endocervical glands, which are responsible for its mucus secreting property. These columnar cells merge and transform into squamous cells of the ectocervix at the squamocolumnar junction located almost at the external orifice of the cervix in perimenarche as well as perimenopausal women and everting over the ectocervix in the form of an ectropion in women of reproductive age, which appears as a prominent reddish layer. The squamocolumnar junction is located in the endocervical canal in post-menopausal women and hence cannot be viewed during visual examination[8].

This variation in the location and distance of the squamocolumnar junction with respect to the external orifice in women of different age and parity occurs due to squamous metaplasia, where the mucus membrane over the ectropion is distorted upon contact with acidic medium, resulting in the replacement of the glandular columnar epithelium by metaplastic squamous epithelium, thereby causing an ascending shift of the squamocolumnar junction towards the internal orifice. It can also be related to the size of the cervix, which is larger and wider in women of reproductive age due to estrogen production in comparison to that of a premature cervix in perimenarche women and shrunken cervix in perimenopausal and postmenopausal women due to reduced estrogen levels. The squamous metaplasia is a stepwise process where the small spherical cuboidal cells appear as reserve cells, which further develop into a single layer of glycogen-devoid immature squamous cells followed by formation of a fully mature glycogen-rich keratinised stratified squamous ectocervix. Sometimes, the metaplastic squamous epithelium develops over remnant columnar cells, causing the obstruction of crypt openings and resulting in the formation of cysts containing the columnar epithelium, called nabothian cysts, within which mucus may be entrapped in some cases causing distention of the cysts and providing an ivory-whitish appearance of the cysts upon visual inspection. This region of development of metaplastic squamous epithelium is called the transformation zone, which can be identified by the location of nabothian cysts[8].

IV. Human Papillomavirus (HPV)

Although Human Papillomavirus (HPV) is often eliminated from the body by the host immune system within a span of 2 years, it is found to be virtually the only cause for development of cervical cancer, exhibiting very few to nil signs and symptoms of the disease, which makes it challenging to identify[6]. HPV is a sexually transmitted virus that is found to infect the genitals of both males and females as well as the linings of mouth and throat, causing genital warts and a number of cancers, of which cervical cancer is one. More than 200

strains of HPV have been identified, which have been grouped as alpha, nu/mu, beta and gamma genera on the basis of their viral genomic structure and invasiveness into the epithelium[9]. Of these, 40 strains are sexually transmitted, and are categorised as low-risk (belonging to beta and gamma genera) and high-risk (alpha) viruses by the International Agency for Research on Cancer, based on their ability to cause carcinogenesis[10]. Low-risk types include the HPV strains, namely, 6, 11, 42, 43, 44, 54, 61, 70 and 81, which usually result in non-malignant lesions over or around the genitals and anus of both men and women, whereas the high-risk HPV strains include 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82, that cause neoplasia, of which strains 16 and 18 are most oncogenic and are the underlying cause for over 75% of cervical cancers. Approximately 90-100% of the genital warts in both sexes are found to be caused by HP strains 6 and 11. A study revealed that about 20-50% of the low-risk HPV infections are often accompanied by high-risk HPV co-infection, making the treatment process further complicated [11].

HPV-mediated Carcinogenesis

The risk of infection by HPV commences within a few days after sexual intercourse. HPV infection begins with the invasion of basal epithelial cells of the cervix. The basal epithelial cells, under normal circumstances, proliferate and migrate to the superficial layers, where they differentiate and undergo senescence as part of the apoptosis process. The HPV block the apoptosis of epithelial cells and cause their malignant transformation by encoding two oncogenic proteins, E6 and E7, which interact with the tumor suppressor genes (TSGs) of TP53 and retinoblastoma family members (namely RB1, RBL1 and RBL2) respectively to enhance cell proliferation and extend cell cycle, enabling the virus to utilise the basal epithelial cell proliferative mechanism to multiply and migrate to the superficial layers of the epithelium, where the L1 and L2 capsid proteins are expressed as an indication of the assembly of viral components into virions, a process which takes 2-3 weeks. In case of the high-risk HPV strains, the E6 and E7 proteins are extensively potent in inhibiting cellular apoptosis, due to which the cell differentiation which is essential for the maturation and release of the virions is inhibited, resulting in the progression of infected malignant lesion into an invasive carcinoma. This ultimately results in an absolute lack of any necrotic or viraemic phase to trigger any immune response at the cervical epithelium[12].

The process of carcinogenesis is further simplified by the immune evasive ability of the high risk E6 and E7 proteins which interfere with toll-like receptor 9 transcription involved in activation of antigen-presenting cells, TAP-1 expression involved in activation of certain cytotoxic T-cells, IRF-1 and IRF-3 expression involved in the synthesis of interferons and the proinflammatory mediator TNF-alpha, causing their downregulation in association with the upregulation of anti-inflammatory cytokines like IL-10, resulting in complete evasion of the immune response at the already poorly immune-scrutinised superficial epithelial layers of cervix. As the tumor size increases, the pressure levied by the host's immune system results in accumulation of further genetic alterations at the site of the pre-cancerous lesion, such as inhibition of MHC-1, diminished antigen-processing ability, immunity to T-cell mediated cytotoxicity, increased production of immunosuppressive cytokines, ultimately resulting in the advancement of the lesion from precancerous to cancerous stage[12].

HPV can also infect the immature metaplastic squamous cells, causing dysplasia and development of precancerous lesions[8].

Host Innate Immune Response

The host immune system is highly efficient in clearing HPV from the body within 12 months of infection, in spite of the plausible immune evasion by the virus. Evidence for the role of both, humoral and cell mediated immunity, in the self-limiting nature of the infection in many people have been found through various tests. The fact that people with existing HIV infection are more susceptible to cervical cancer caused by HPV is an evidence in itself for the role of T-cell mediated immunity in prevention of the disease, which has further been emphasised by various other longitudinal non-interventional studies. Antibodies against LI capsid protein of the virus, both strain-specific and non-specific types, have been identified in the peripheral smears of the previously as well as currently infected persons, which can be seen and measured 6 months after the infection and persist for upto 5 years, sometimes for a lifetime, and hence can be used as a diagnostic aid for detection of existing or past infection[12]. Infection into basal epithelial cells, which are the stem cells, may lead to longer persistence of the infection and make it challenging for achieving complete remission without radical hysterectomy, while infection into the differentiated keratinocytes is much easier to resolve by the host immune system as well as by other therapeutic or surgical interventions[13]. Owing to this effective anti-cancerous response, it takes about 15-20 years for cervical cancer to develop after infection in healthy women, and upto 5-10 years in immunocompromised women[14].

V. HPV Vaccination

The major preventive strategy for cervical cancer is HPV vaccination. There are three HPV vaccines currently available in the market; the bivalent vaccine Ceravix, the quadrivalent vaccine Gardasil, and the non-valent vaccine Gardasil 9. The preliminary targets of HPV vaccination programmes are girls aged 9-14 years old with a 2 Dose schedule, Girls and women over 15 years are advised to receive a 3 Dose schedule. All three vaccines protect against types 16 and 18, which have a high oncogenic burden, and are responsible for about 60-70% of all cervical cancers. The non-valent vaccine Gardasil 9 has coverage against 5 more high-risk HPV strains and can prevent upto 80-90% of cervical cancers. The HPV vaccines have proven to be safe and highly beneficial to induce strong direct or cross-immuntiy protection against HPV. With the recent advancements and development of these vaccines, there is scope to almost completely eliminate cervical cancer among immunized women, especially in the context of continued cervical cancer screening programs and wide population vaccine coverage[15].

In the recent past, HPV vaccines have been approved in 129 countries and over 270 million doses of the vaccine have been supplied worldwide. The most substantial estimates report a global HPV vaccine coverage of 6.1% among females aged 10-20 years, with a 33.6% coverage in more developed countries. Successful coverage(i.e., >80-90%) among the selected population has been attained in 18 countries(Australia, Bhutan, Iceland,Malaysia, Mexico and Seychelles etc..) basically through school based programs, supported by health-care outreach[15].

The countries with the biggest populations globally, India and China, currently do not have a population-based program for HPV vaccination. However, according to the recent data published by the Catalan Institute of Oncology and the IARC, India has one of the world's largest incidences of cervical cancer. Approximately 122,000 Indian women are diagnosed with cervical cancer and around 67,000 die from this disease each year. It is estimated that the cost-effectiveness of various HPV related cancer prevention strategies i.e.,vaccination before 12 years of age and mandatory cancer screening for women above 30 years of age can lower the risk of cervical cancer. And also, if a bivalent vaccine coverage of 70% is assumed, there would be a 44% mean decrease in the lifetime risk of HPV related cancer. Recommendations about inclusion of combined vaccine and screening program has been made by the medical bodies and the ICMR, which updated the government about inclusions into the Universal Vaccination Program[16].

However, HPV vaccination alone will not eradicate cervical cancer, even if it is implemented widely. There are over 100 HPV variant serotypes which have been identified till date, and out of these 100 variants only 7 most oncogenic strains are covered by the HPV vaccines which are currently available in the market, Other less oncogenic strains still remain as a matter of concern. With the existing HPV vaccines available in the market 70-75% of all cervical cancers can be prevented,given in a scenario where 80-100% of the target population coverage is achieved, though such vaccination coverage relies on vaccination rates currently. But the vaccination rate is very much underachieved in many parts of the world. Therefore, it is of great importance to retain and more-effectively implement cervical cancer vaccination and screening as a vital element of cervical cancer prevention and control[16].

VI. Screening And Prevention Of Cervical Cancer

Upon infection by high-risk HPV strains, the viral genome may get integrated within the host cellular genome, leading to the generation of cervical neoplastic cells, which proliferate to form cervical intracellular neoplasia (CIN), also called squamous intracellular neoplasia (SIN) or, in simple terms, precancerous lesions, which can be graded into CIN1, CIN2 and CIN3 in increasing order of dysplasia. CIN1 is also referred to as low-grade squamous intracellular neoplasia (LSIN) as the lesions are often transient and self-limited which do either regress within a short span or do not progress to higher stages, while CIN2 and CIN3 are grouped under high-risk SIN (HSIN), represented as CIN2+, due to increased risk of the lesions to develop into invasive cervical cancer. This progression from CIN to invasive cervical cancer often takes 15-20 years in women with normal immune response and about 5-10 years in women with diminished or compromised immune response, which provides an excellent window for early detection of HPV infected precancerous lesions and prevention of their progression into invasive cervical cancer[8]. Screening programmes implemented across the continents constitute a strategy to identify the infection or precancerous lesions in their early stages, where the treatment modalities ensure complete eviction of the infection or lesions, causing an overall reduction in the incidence and mortality as a result of cervical carcinoma, which has been depicted by a promising decline in the cases and deaths of cervical neoplasm over the years by about 50-70% in various developed countries where this strategy has been adapted[17].

India being a country with regional diversities in terms of socio-economic status, culture and religious practices, makes it challenging to provide uniform screening services throughout the country, owing to the requisites of the screening tests needed for maximum accuracy and precision of the results. Hence, the screening programme in India is implemented differently in different regions in accordance with the resource availability

in urban and rural areas.

The WHO recommended techniques available in India for the purpose of early detection of precancerous or invasive lesions of cervical neoplasia include microscopic examination through cytologic analysis, called Pap Smear, HPV test and Visual examination of the cervix[17].

Cytology or Pap Smear

Cytological examination, popularly referred to as Papanicolaou (pap) smears is the primary and first line method used for screening sexually active women for presence of precancerous or cancerous lesions of the cervix, that involves collection of the specimen from the ectocervix of the women under study, during the proliferative period of the cervix i.e. at least 5 days after onset of menstrual cycle, by using a wooden spatula, which can be performed by a nurse or the patient herself and is of 3 types based on the technique involved in analysis of the sample- conventional, liquid-based and automated cytology[18].

While the **conventional or direct cytology** involves collection of the cells from the ectocervix followed by mounting and fixing the samples on a glass slide using ethanol, staining and viewing of the cells under a microscope, **liquid-based cytology (LBC)** utilises an alcohol-based fluid medium for the preservation of the samples and the resulting suspension is then processed and applied onto a glass slide in the form of a thin uniform debris-free layer for viewing under the microscope, which provides an advantage of increased reliability due to the possibility of testing the complete sample as well as due to elimination of factors that hinder the assessment process, such as debris, entrapped air and superimposed cells, thereby reducing the chances of inadequate smears from 13.8% in pap smear to 5.7% in LBC[19]. The sensitivity of pap smear in the detection of HSIL and invasive cervical neoplasm based on Indian studies were found to be about 70%[18]. In spite of LBC showing greater reliability, the procedure is expensive due to the requirement of a collection kit and automated instrumentation for the purpose of preparation of the slides, in comparison to direct pap smear, which does not require any such instrumentation[20].

Precancerous cells can be identified and marked by comparison with normal intermediate squamous epithelial cells of the ectocervix, where the former have a larger nucleus-cytoplasmic ratio whose magnitude corresponds with the severity of neoplasia, larger magnitude representing greater severity. Other morphological changes such as hyperchromasia and irregular cell boundaries can also be distinctively noticed in precancerous lesions. In order to differentiate them from other non-cancerous lesions, a repeat sampling can be performed after application of estrogen vaginal cream[20].

HPV Test

The gold standard for the detection and identification of specific types of HPV is enabled by the Human Papillomavirus test (HPV test), that recognises the DNA or RNA of the carcinogenic virus by utilising an array of molecular assays, which include nonamplified hybridization techniques such as southern transfer hybridization (STH), dot blot hybridization (DB) and in situ hybridization (ISH), signal amplified hybridization assays such as hybrid capture (HC) assays as well as target amplification assays such as polymerase chain reaction (PCR), in situ PCR and Reverse Transcriptase PCR (RT-PCR) along with nucleic acid sequence based amplification (NASBA), of which the latter 2 aid in the detection of RNA while remaining techniques identify the DNA molecules[21].

Currently, 5 tool have been approved by the US Food and Drug Administration (US FDA), the first and foremost one being Hybrid Capture II (HC II) HPV DNA Assay by Digene, a HC based assay which detects the DNA of 13 types of HR virus by nucleic acid hybridization with signal amplification using microplate chemiluminescent detection, followed by Cervista HPV HR test and Cervista HPV 16/18 test by Hologic that are based on the principle of a signal amplification method of Invader chemistry, Cobas HPV test by Roche Molecular Systems that uses PCR amplification for the detection of the viral DNA, and the most recently approved tool called Aptima HPV test that identifies HPV mRNA by Transcription-mediated Amplification (TMA) along with Hybridisation Protection Assay (HPA). While HC-II HPV DNA assay recognises 13 different strains of HR HPV, which include types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68, Cervista HPV HR, Aptima and Cobas HPV tests also detect type 66 in addition to the above mentioned types. Additional tests commercially available in India include careHPV test by Qiagen[21].

Visual Inspection

Visual inspection of the cervix involves the low-technology modalities for cervical cancer screening which were introduced and investigated for their accuracies in the detection of cervical cancer as a substitute to the gold-standard cytological testing in low-resource regions of low to middle income countries, inspired by the age old Schiller's iodine test which was used decades ago for this purpose and aborted after the advent of novel screening methods. The available visual inspection techniques include Visual Inspection after application of 5% acetic acid (VIA) and that after application of Lugol's iodine (VILI), whose test results are instantly available

and interpretation is based on the colour changes observed in the cervix post treatment with 5% acetic acid or Lugol's iodine.

Prior to treatment of the cervix with 5% acetic acid or lugol's iodine, the external genitalia and perineal region of the women should primarily be examined thoroughly for the presence of any signs of excoriations, edema, vesicles, papules, sores, ulceration and warts as well as for the presence of swelling in the inguinal or femoral region. The position of the anatomical regions, such as the squamous epithelium, the columnar epithelium, the squamocolumnar junction and the transformation zone along with the ectropion, cervical polyp, nabothian cysts, healed lacerations on the cervical lips, leukoplakia, condylomata and signs of cervicitis if any should be noted with aid of their characteristic colourations as viewed under naked eye and sufficient illumination. Invasive cancerous lesions may appear in the form of erythematous granular regions in their early stages or as an exophytic growth with polypoid or papillary ulceroproliferative mass in their advanced stages, both of which bleed on touch, and may be associated with foul smelling discharge as a result of infection[22].

In case of **Visual Inspection after application of 5% acetic acid (VIA)**, the cervix is keenly observed for the presence of white lesions, called acetowhite areas, with respect to their size, colour intensity and uniformity, margins and location, which determine the nature and extent of precancerous lesions. Prior to application of acetic acid, any vaginal discharge should be cleared off with a cotton swab to avoid false-positive assessment. VIA is based on the principle that acetic acid causes the precipitation of cellular proteins which are present abundantly in actively proliferating neoplastic cells, resulting in the appearance of acetowhite regions, which are often restricted to the transformation zone in CIN and are present all over the cervix in case of cancer. Although acetowhite can also be observed in other conditions associated with abundant nuclear proteins, such as immature squamous metaplasia, in healing and regenerating epithelium post inflammation, leukoplakia and condyloma, they can be differentiated by observing the dense, thick, opaque and well-demarcated acetowhitening associated with CIN and neoplastic cells in contrast to the pale, thin, translucent acetowhitening with ill-defined margins which often fade away soon in case of immature squamous metaplasia and inflammation and regenerating cells as well as the grayish-white discolouration observed in case of leukoplakia and condylomata[22].

When performing **Visual Inspection after application of Lugol's Iodine (VILI)**, the cervix is observed for the presence of dense, thick, bright, mustard or saffron yellow iodine non-uptake areas in the transformation zone, close to the squamocolumnar junction or to the orifice if the squamocolumnar junction is not seen, which indicates the presence of precancerous lesions, with entire cervix appearing dense yellow in advanced CIN. Invasive cancerous lesions also appear densely yellow. Discrete, ill-defined and thin regions exhibiting no colour change or brown colour or a slight hint of yellow coloured region away from the squamocolumnar junction are indicative of other inflammatory and non-malignant conditions. In normal cervix, the squamous metaplastic and epithelial cells being abundant in glycogen, take up the iodine and turn to mahogany brown or black, which is lacking in case of columnar epithelial cells, immature squamous metaplastic cells, condylomatous and leukoplakic cells which appear in their original colours of reddish-pink, as well as in case of CIN and invasive cancerous cells which appear mustard of saffron yellow, thereby clearly differentiating the precancerous and cancerous cells from the non-malignant cells[22].

VII. Diagnosis of Cervical Cancer

Early screening and diagnosis of cervical cancer plays a major role in optimal therapy and helps to prevent further complications. Approximately 50% to 80% of the incidence of the malignancy has substantially reduced after organizing screening programs [23]. Women with positive screening results are referred for diagnosis, for which by different methods like coloposcopy, Biopsy, Endocervical curettage (ECC) etc, can be used.

Colposcopy, which utilizes a colposcope, for visualizing the pre-cancerous lesion after the application of 5% acetic acid solution to the cervix, has a has limitations that it has low reproducibility of colposcopic impressions and inaccurate biopsy placement, in addition to failure to detect 30- 50% of high grade cervical precancers. This can be overcome by the adoption of multiple lesion-directed biopsies. Endocervical curettage (ECC),which is a method of biopsy that employs the use of a curette, for scraping endocervical lining can be utilized where colposcopic examination is inadequate or no significant lesion is found in non-pregnant women. However, it depicts lesser benefits in menopausal women, due to stenotic cervix and is contraindicated in pregnant women[24,25].

Imaging techniques play a vital role in diagnosing, staging, planning of treatment and prediction of prognosis. The National Cancer Comprehensive Network (NCCN) guidelines for cervical cancer recommend magnetic resonance imaging (MRI) or computed tomography of the pelvis, abdomen and/or chest as the primary diagnostic workup for the evaluation of the extent of local tumor and distant metastasis, with/without a whole body. A whole body positron tomography can be utilized as an alternative imaging technique. Many studies have shown the diagnostic importance of the above non-invasive technique, in addition to that of 18F- fluoro

2-deoxy-D-glucose (18F-FDG) and diffusion-weighted magnetic resonance imaging (DW-MRI), in the identification of lymph node metastasis in the patients. PET or PET/CT shows dual benefits of anatomic and functional imaging, and has been useful in localizing areas of increased FDG uptake with improved anatomic specificity. DW-MRI shows tissue diffusion properties and therefore provides detailed structural information by using the apparent diffusion coefficient (ADC). Transrectal ultrasound (TRS) and transvaginal ultrasound (TVS) also provide complete and accurate information on local tumor extent. Among all the non-invasive modalities, DWI-MRI has shown to have highest sensitivity and specificity[26-27]. Polarimetric imaging, another novel imaging modality, uses linearly polarized light to observe the cervix through a linear analyser and can be used as an alternative to colposcopy[24].

Liquid biopsy, a test done to detect the biomarkers HPV E6, HPV E7, Mini chromosome maintenance (MCM), Cell division cycle protein 6 (CDC6), p16INK4A, Squamous cell carcinoma antigen (SCC), cell proliferation markers like proliferating cell nuclear antigen (PCNA), ki-67, cyclin-D, cyclin-E, DNA Topoisomrase II α (TOP2A) and telomerase, helps to improve the efficacy of early diagnosis and prognosis of cervical cancer and to examine metastasis[28]. While E7 and L1 detected in about 62% of patients aid in determining the prognosis and estimating the risk of relapse of the carcinoma, TOP2A/MCM2 can differentiate between LSIL and HSIL and are detected in about 93.8% of patients. The biomarkers of $p16^{INK4a}$, cyclin E1, Ki-67 can be found in 90%, 91%, 89.3% and 88.9% of the patients respectively[29,30]. Circulating exosomal miR- 125a- 5p is a novel biomarker which can be used for diagnosis of the malignancy,in addition to the presence of low concentrations of exosomes, which is still under clinical trials and require more samples to support the results[31].

Other novel techniques by which cervical cancer can be detected are Multi–scale multi feature convolutional neural network (M^2CNN), Intelligent Knife (iKnife) to differentiate, laser induced breakdown spectroscopy (LIBS), involving atomic emission spectroscopy coupled with principal component analysis (PCA) and Support vector machine (SVM)[32-34].

VIII. Staging of Cervical Cancer

For the purpose of staging tumors, the size of the tumor along with the nodes involved as well as the distant spread of the cancerous lesion are evaluated. The Lymphatic system drain their contents into the Parametrial, Obturator, Internal iliac (hypogastric), External iliac, Common iliac and Sacral Presacral lymph nodes associated with the cervix, which may get infiltrated by the cervical malignant cells and are resected followed by histopathologically examined for staging the cancer. In case of metastatic lesions, the carcinoma is found to be mostly spread to the para-aortic, supraclavicular node and mediastinal nodes, lungs, peritoneal cavity, and skeleton. Cervical cancer staging can be done in 2 ways- clinical staging, where the staging is performed former to initiation of therapy by means of clinical, visual or radiographic examination, and pathological staging, where the staging is done based on the histopathological characteristics of the resected tumor and lymph nodes as examined after their surgical removal. Staging includes only the invasive malignant lesions and does not consider the precancerous lesions[35].

FIGO Staging is the form of clinical staging technique adopted by the International Federation of Gynecology and Obstetrics (FIGO) in the year 2008 which categorises the carcinoma on the basis of tumor size and spread in the absence of histological examination, and is widely as well as primarily used for the staging of cervical cancer in order to maintain uniformity in the diagnostic category of the disease among women who undergo surgical resection as well as those who do not, the latter comprising of a larger proportion due to detection of the carcinoma in the advanced non-resectable stages[35].

The classic TNM staging is the pathological staging system which can be utilised in addition to FIGO staging after surgical resection of the tumor with or without the lymph nodes in early stage cervical carcinomas, followed by their histopathological examination for tumor size, nodal involvement and degree of spread. The FIGO staging classification in relation to the TNM staging is described in the table below[35].

Table no 1: FIGO staging classification of cervical cancer

FIGO STAGES	TNM STAGING			DESCRIPTION
	T	N	M	
Stage 0*	Tis	N0	M0	Carcinoma in situ (preinvasive carcinoma)
Stage I	T1	N0	M0	Cervical carcinoma confined to uterus (extension to corpus should be disregarded)

Stage IA	T1a	N0	M0	Invasive carcinoma diagnosed only by microscopy. Stromal invasion with a maximum depth of 5.0 mm measured from the base of the epithelium and a horizontal spread of 7.0 mm or less. Vascular space involvement, venous or lymphatic, does not affect classification
Stage IA1	T1a1	N0	M0	Measured stromal invasion 3.0 mm or less in depth and 7.0 mm or less in horizontal spread
Stage IA2	T1a2	N0	M0	Measured stromal invasion more than 3.0 mm and not more than 5.0 mm with a horizontal spread 7.0 mm or less
Stage IB	T1b	N0	M0	Clinically visible lesion confined to the cervix or microscopic lesion greater than T1a/IA2
Stage IB1	T1b1	N0	M0	Clinically visible lesion 4.0 cm or less in greatest dimension
Stage IB2	T1b2	N0	M0	Clinically visible lesion more than 4.0 cm in greatest dimension
Stage II	T2	N0	M0	Cervical carcinoma invades beyond uterus but not to pelvic wall or to lower third of vagina
Stage IIA	T2a	N0	M0	Tumor without parametrial invasion
Stage IIA1	T2a1	N0	M0	Clinically visible lesion 4.0 cm or less in greatest dimension
Stage IIA2	T2a2	N0	M0	Clinically visible lesion more than 4.0 cm in greatest dimension
Stage IIB	T2b	N0	M0	Tumor with parametrial invasion
Stage III	T3	N0	M0	Tumor extends to pelvic wall and/ or involves lower third of vagina, and/or causes hydronephrosis or non-functioning kidney
Stage IIIA	T3a	N0	M0	Tumor involves lower third of vagina, no extension to pelvic wall
Stage IIIB	T3b T1-3	Any N N1	M0 M0	Tumor extends to pelvic wall and/ or causes hydronephrosis or non-functioning kidney, with or without regional lymph node metastasis
Stage IVA	T4	Any N	M0	Tumor invades mucosa of bladder or rectum, and/or extends beyond true pelvis (bullous edema is not sufficient to classify a tumor as T4), with or without regional lymph node metastasis
Stage IVB	Any T	Any N	M1	Tumor of any size associated with or without regional lymph node metastasis and with distant metastasis (including peritoneal spread, involvement of supraclavicular, mediastinal, or paraaortic lymph nodes, lung, liver, or bone)

* Note: FIGO no longer includes Stage 0 (Tis).

VII. Treatment of Cervical Precancerous Lesions

World Health Organisation (WHO) has replaced the traditional process of screening and diagnosing through cytology, colposcopy, biopsy and histological confirmation of pre-cancerous lesion by a more efficient and time-saving method of screen-and treat, where treatment is provided for precancerous lesion following a positive screen test during the same clinical visit, thus enabling the provision of immediate treatment for the precancerous lesion, and overcoming the drawback of loss to follow-up situation due to requirement of lesser clinical visits[17,36].

The main objective behind development of screen-and-treat procedure was to decrease the morbidity and mortality due to cervical cancer in a cost-effective method with considerably lesser adverse effects of the

treatment, which is extremely necessary, especially so in case of lower-to-middle income countries, including India[17].

The methods for treating CIN2+ have advanced since the early 1970s, from a complex surgical method, hysterectomy, being the only acceptable procedure for treatment until the 1970s, to widely used simpler methods of Cold-knife Conization (CKC), loop electrosurgical excision procedure (LEEP), cryotherapy and thermal coagulation methods since the 1980s and early 2000s. However, all the methods will require the use of 5% acetic acid solution or lugol's iodine solution in order to visualise and demarcate the precancerous lesion and the transformation zone[37]. While both, CKC and LEEP require the use of local anaesthesia, the method of CKC utilises a cold knife to excise a cone of the precancerous lesion including the transformation zone, LEEP employs the use of radiofrequency electric current through electrode loop made of very fine stainless steel of tungsten wire to cut across the transformation zone of the lesion, which also enables hemostasis by providing desirable level of coagulation and preventing bleeding, therefore being a technically superior procedure[38,39]. In either case, specimens are available for further histological examination of the pathological cervical tissue. The techniques of cryotherapy and thermal coagulation involve the application of extreme temperatures to the cervical precancerous tissue using a probe in order to initiate necrosis, the former utilising extreme cold and the latter employing extreme hot temperatures to cause ablation of the infected tissue. While both the therapies are equally effective, cryotherapy is more predominantly employed due to its cost-effectiveness[37].

The World Health Organisation (WHO) recommends cryotherapy as the first-line treatment technique for screen positive women who depict a clear and complete precancerous lesion which covers not more than 75% of the ectocervix, along with squamocolumnar junction. In conditions where there is the availability and feasibility of employing LEEP and where the lesion extends into the endocervical canal, LEEP is the technique of choice**[17].**

VIII. Management of Malignant Cervical Cancer

The International Federation of Gynaecology and Obstetrics system of staging (FIGO staging) of cervical cancer is currently used as the basis for the treatment[40].

Treatment of Stage IA Cervical Carcinoma

Treatment choice for women with stage IA1 cervical cancer who wishes to retain fertility with at most 1 or no risk factor is conisation and on histological examination the surgical margin should be tumor cell free. For women with stage IA1 cervical cancer with risk factor of 2 or more and who wishes to retain fertility, even though conisation is adequate, other treatment option such as trachelectomy, along with either pelvic sentinel lymph node biopsy, or systematic pelvic lymphadenectomy can be considered[41]. Women who do not want to retain fertility or of non reproductive age, the treatment of choice is abdominal or vaginal extrafascial hysterectomy[42].

In stage IA2 of cervical cancer, 2-8% is the lymph-node metastasis risk[42]. Primary radical hysterectomy, modified radical hysterectomy with pelvic lymphadenectomy or primary radiotherapy are the treatment options in this stage[40]. Women with desire to get pregnant and have no risk factor or maximum of 1 risk factor, the choice of treatment is radical trachelectomy or cone biopsy plus pelvic lymphadenectomy. In women who don't want to retain fertility, with no or maximum of 1 risk factor the treatment of choice is simple total hysterectomy[41]. The treatment option for more women with more than 1 risk factor is radical hysterectomy with pelvic node dissection for women of non reproductive age or who doesn't wish to retain fertility and radical trachelectomy with laparoscopic pelvic node dissection for women with desire to get pregnant1. In women who deny surgery or are inoperable, Pelvic external beam radiation with brachytherapy is the treatment choice[43].

Treatment of Stage IB Cervical Carcinoma

In Stage IB1 cervical cancer, the treatment of choice is radical hysterectomy with pelvic and para-aortic lymphadenectomy or primary radiotherapy[44]. With no or 1 risk factor, radical trachelectomy is the choice of surgery in women with wish to retain fertility. Cone biopsy with pelvic lymphadenectomy or sentinel biopsy can also be considered. Women with more than 1 risk factor, individualised treatment is considered. Neoadjuvent chemotherapy followed by trachelectomy can be considered. In women who are not of childbearing age, hysterectomy is the treatment option[41]. The cure rates for both surgery and radiation therapy are the same. External- beam radiation of 45 to 50 Gy is administered preceded by intracavitary radiation. Recent studies have shown that concurrent platinum-based chemotherapy with radiation therapy is beneficial[45].

Radical hysterectomy, pelvic and para-aortic lymphadenectomy, and adjuvant radiotherapy or cisplatin-based chemoradiotherapy, 45 to 50 Gy of external beam pelvic radiotherapy and vaginal brachytherapy preceded by simple hysterectomy, or definitive concurrent chemoradiation are the treatment option for stage IB2[44,45]. Chemotherapy by 75mg/m2 of Cisplatin administered intravenously for over 4 hours of three cycles at 3 week interval or 4000mg/m2 of 5-fluorouracil administered intravenously for over 96 hours of three cycles at

3 week interval are currently used in patients with stage IB[45].

Treatment of Stage IIA Cervical Carcinoma

Based on the involvement of cervix and vagina, treatment is individualised for patients. Chemoradiotherapy is usually preferred but surgery like hysterectomy, lymphadenectomy, and upper vaginectomy is preferred when the tumor cell extension into the vaginal fornix is minute[42].

Treatment of Stage IIB, III and IVA Cervical Carcinoma

Treatment with only radical surgery after the extension of a cancer cell beyond the cervix is not plausible. The National Cancer Institute recommended chemotherapy along with radiotherapy as standard treatment for stage IIB-IVA cervical cancer[42]. 40 mg/m2 of cisplatin IV once a week along with 1.8-2 Gy per fraction of 4-6 cycles of radiation therapy or 50-75 mg/m^2 of cisplatin on day 1 with 1000 mg/m^2 of 5-fluorouracil continuous IV infusion over 24 hours on day 1-4 every 3 weeks for 3-4 cycles along with 1.8-2 Gy of radiation therapy for total of 45Gy or 40 mg/m^2 of cisplatin IV once a week 125 mg/m^2 of gemcitabine weekly for 6 weeks along with total of 50.4 Gy in 28 fractions of radiation therapy preceded by 30 to 35 Gy in 96 hours of brachytherapy followed by two adjuvant 21-day cycles of 50 mg/m^2 of cisplatin on day 1 with 1000 mg/m^2 of gemcitabine on days 1 and 843.

Treatment Of Stage IVB Cervical Carcinoma

Chemoradiotherapy is considered to control metastasis in patient with stage IVB acceptable performance status[42]. 15 mg/kg IV of Bevacizumab over 30-90 min on day 1 with 50 mg/m^2 of cisplatin IV over 60 min on days 1 or 2 with 175 or 135 mg/m^2 of paclitaxel IV over 3 hours or 24 hours on day 1 every 3 week or 135 mg/m^2 of paclitaxel IV over 24 hours on day 1 preceded by 50 mg/m^2 of IV on day 2 every 3 week or 15 mg/kg of Bevacizumab IV over 30-90 min along with 175 mg/m2 of paclitaxel IV over 3 hours on day 1 with 0.75 mg/m^2 of topotecan IV over 30 min on days 1-3 every 3 week or 175 mg/m^2 of Paclitaxel IV over 3 h preceded by carboplatin area under the curve (AUC) 5 IV over 30 minutes on day 1 every 3 week are the first line therapy for stage IVB cervical cancer[43].

IX. Conclusion

Despite the multiple advances in the areas of screening, diagnosis, prevention and treatment of cervical cancer and the subsequent reduction in morbidity and mortality due to the carcinoma, it remains to be the leading cause of death in women, more so in case of lower and middle income countries such as India, due to the poor acceptance of screening and vaccination techniques among various cultures, and the inability to afford preventive or curative treatments for the malignancy. There is an obligatory requirement of methods to upscale the horizon of screening and vaccination programmes, which can be successful to its best extent only if ways to provide awareness among the women and to overcome the barriers for acceptance of the preventive modalities such as that of religion, culture, knowledge, etc can be exercised, which will enable the involvement of the public in the effective implementation of vaccination and screening programme. Along with efforts to optimise acceptance among the people, advent of newer, simpler and cost-effective methods of diagnosis and treatment of the malignant carcinoma is essential to quell the obstacle of financial insufficiency for its successful eradication. From this review it is clear that HPV screening along with vaccination should be widely implemented, supported and be accepted at national level in countries with high incidence and death rate of cervical cancer. Upon adapting the aforesaid modalities, India can gloriously overcome the burden of cervical cancer as a potential cause of mortality.

References

[1]. https://www.who.int/health-topics/cancer#tab=tab_1
[2]. https://www.who.int/health-topics/cervical-cancer#tab=tab_1
[3]. https://www.nccc-online.org/hpvcervical-cancer/cervical-cancer-overview/
[4]. https://gco.iarc.fr
[5]. Small W, Bacon MA, Bajaj A, Chuang LT, Fisher BJ, Harkenrider MM, et al. Cervical cancer: A global health crisis. Cancer. 2017;123(13):2404–12.
[6]. de Sanjosé S, Brotons M, Pavón MA. The natural history of human papillomavirus infection. Best Pract Res Clin Obstet Gynaecol. 2018;47:2–13.
[7]. Kessler TA. Cervical Cancer: Prevention and Early Detection. Semin Oncol Nurs [Internet]. 2017;33(2):172–83. Available from: http://dx.doi.org/10.1016/j.soncn.2017.02.005
[8]. Sankaranarayanan R, Wesley R. A practical manual on visual screening for cervical neoplasia (IARC technical publication N° 41). IARCPress [Internet]. 2005;(41):41. Available from: press@iarc.fr
[9]. de Villiers EM. Cross-roads in the classification of papillomaviruses. Virology. 2013;445(1–2):2–10.
[10]. Doorbar J, Quint W, Banks L, Bravo IG, Stoler M, Broker TR, et al. The biology and life-cycle of human papillomaviruses. Vaccine [Internet]. 2012;30(SUPPL.5):F55–70. Available from: http://dx.doi.org/10.1016/j.vaccine.2012.06.083
[11]. Maas N, Robinia KA. Gynecologic cancers. In: Schuiling KD, Kikis FE, eds. Women's Gynecologic Health. 3rd ed. Burlington, MA: Jones and Bartlett Learning; 2017:662-667.

[12]. Crosbie EJ, Einstein MH, Franceschi S, Kitchener HC. Human papillomavirus and cervical cancer. Lancet [Internet]. 2013;382(9895):889–99. Available from: http://dx.doi.org/10.1016/S0140-6736(13)60022-7
[13]. Roden RBS, Stern PL. Opportunities and challenges for human papillomavirus vaccination in cancer. Nat Rev Cancer [Internet]. 2018;18(4):240–54. Available from: http://dx.doi.org/10.1038/nrc.2018.13
[14]. https://www.who.int/en/news-room/fact-sheets/detail/human-papillomavirus-(hpv)-and-cervical-cancer
[15]. Perez S, Zimet GD, Tatar O, Stupiansky NW, Fisher WA, Rosberger Z. Human Papillomavirus Vaccines: Successes and Future Challenges. Drugs [Internet]. 2018;78(14):1385–96. Available from: https://doi.org/10.1007/s40265-018-0975-6
[16]. Gallagher KE, LaMontagne DS, Watson-Jones D. Status of HPV vaccine introduction and barriers to country uptake. Vaccine [Internet]. 2018;36(32):4761–7. Available from: https://doi.org/10.1016/j.vaccine.2018.02.003
[17]. WHO. Guidelines for screening and treatment of precancerous lesions for cervical cancer prevention. WHO Guidel [Internet]. 2013;60. Available from: http://www.who.int/reproductivehealth/publications/cancers/screening_and_treatment_of_precancerous_lesions/en/index.html
[18]. Sachan PL, Singh M, Patel ML, Sachan R. A study on cervical cancer screening using pap smear test and clinical correlation. Asia Pac J Oncol Nurs 2018;5:337-41.
[19]. Sankaranarayanan R, Gaffikin L, Jacob M, Sellors J, Robles S. A critical assessment of screening methods for cervical neoplasia. Int J Gynecol Obstet. 2005;89(SUPPL. 2):4–12.
[20]. Canepa M, Patel NR, Garcia-moliner ML. Uterine Cervical Cancer. Uterine Cerv Cancer. 2019;61–87.
[21]. Tsikouras P, Zervoudis S, Manav B, Tomara E, Iatrakis G, Romanidis C, et al. Cervical cancer: Screening, diagnosis and staging. J BUON. 2016;21(2):320–5.
[22]. Sankaranarayanan R, Nessa A, Esmy PO, Dangou JM. Visual inspection methods for cervical cancer prevention. Best Pract Res Clin Obstet Gynaecol [Internet]. 2012;26(2):221–32. Available from: http://dx.doi.org/10.1016/j.bpobgyn.2011.08.003
[23]. Eun TJ, Perkins RB. Screening for Cervical Cancer. Med Clin North Am [Internet]. 2020;104(6):1063–78. Available from: https://doi.org/10.1016/j.mcna.2020.08.006
[24]. Anastasiadou M, De Martino A, Clement D, Liège F, Laude-Boulesteix B, Quang N, et al. Polarimetric imaging for the diagnosis of cervical cancer. Phys Status Solidi Curr Top Solid State Phys. 2008;5(5):1423–6.
[25]. Hui-Chia Liu A, Walker J, Gage JC, Gold MA, Zuna R, Dunn ST, et al. Diagnosis of cervical precancers by endocervical curettage at colposcopy of women with abnormal cervical cytology. Obstet Gynecol. 2017;130(6):1218–25.
[26]. Haldorsen IS, Lura N, Blaakær J, Fischerova D, Werner HMJ. What Is the Role of Imaging at Primary Diagnostic Work-Up in Uterine Cervical Cancer? Curr Oncol Rep. 2019;21(9).
[27]. Liu B, Gao S, Li S. A comprehensive comparison of CT, MRI, positron emission tomography or positron emission tomography/CT, and diffusion weighted imaging-MRI for detecting the lymph nodes metastases in patients with cervical cancer: A meta-analysis based on 67 studies. Gynecol Obstet Invest. 2017;82(3):209–22.
[28]. Yim E-K, Park J-S. Biomarkers in Cervical Cancer. Biomark Insights. 2006;1:117727190600100.
[29]. Cheung TH, Yim SF, Yu MY, Worley MJ, Fiascone SJ, Chiu RWK, et al. Liquid biopsy of HPV DNA in cervical cancer. J Clin Virol [Internet]. 2019;114(February):32–6. Available from: https://doi.org/10.1016/j.jcv.2019.03.005
[30]. Del Moral-Hernández O, Hernández-Sotelo D, Alarcón-Romero L del C, Mendoza-Catalán MA, Flores-Alfaro E, Castro-Coronel Y, et al. TOP2A/MCM2, p16INK4a, and cyclin E1 expression in liquid-based cytology: a biomarkers panel for progression risk of cervical premalignant lesions. BMC Cancer. 2021;21(1):1–13.
[31]. Lv A, Tu Z, Huang Y, Lu W, Xie B. Circulating exosomal miR-125a-5p as a novel biomarker for cervical cancer. Oncol Lett. 2020;21(1):1–6.
[32]. Xu Z, Rao M. A novel M2CNN method for cervical cancer cell recognition. J Appl Sci Eng. 2021;24(2):215–21.
[33]. Tzafetas M, Mitra A, Paraskevaidi M, Bodai Z, Kalliala I, Bowden S, et al. Erratum: The intelligent knife (iKnife) and its intraoperative diagnostic advantage for the treatment of cervical disease (Proceedings of the National Academy of Sciences of the United States of America (2020) 117 (7338-7346) DOI: 10.1073/pnas.1916960117). Proc Natl Acad Sci U S A. 2020;117(31):18892.
[34]. Wang J, Li L, Yang P, Chen Y, Zhu Y, Tong M, et al. Identification of cervical cancer using laser-induced breakdown spectroscopy coupled with principal component analysis and support vector machine. Lasers Med Sci. 2018;33(6):1381–6.
[35]. AJCC Manual of Cancer Staging, 7th edition
[36]. Wentzensen N, Chirenje ZM, Prendiville W. Treatment approaches for women with positive cervical screening results in low-and middle-income countries. Prev Med (Baltim) [Internet]. 2021;144(October 2020):106439. Available from: https://doi.org/10.1016/j.ypmed.2021.106439
[37]. Castle PE, Murokora D, Perez C, Alvarez M, Quek SC, Campbell C. Treatment of cervical intraepithelial lesions. Int J Gynecol Obstet. 2017;138:20–5.
[38]. Activity CE. Conization Of Cervix Contraindications. 2021;1–4.
[39]. https://screening.iarc.fr/colpochap.php?chap=13.php&lang=1
[40]. Kesic V. Management of cervical cancer. Eur J Surg Oncol. 2006;32(8):832–7.
[41]. Brucker SY, Ulrich UA. Surgical Treatment of Early-Stage Cervical Cancer. Oncol Res Treat. 2016;39(9):508–14.
[42]. Panici PB, Angioli R, Penalver M, Pecorelli S. Cervical cancer. Chemother Gynecol Neoplasms Curr Ther Nov Approaches. 2004;361:547–54.
[43]. https://emedicine.medscape.com › 2005259-overview
[44]. Cohen PA, Jhingran A, Oaknin A, Denny L. Cervical cancer. Lancet [Internet]. 2019;393(10167):169–82. Available from: http://dx.doi.org/10.1016/S0140-6736(18)32470-X
[45]. Lu KH, Burke TW. Early cervical cancer. Curr Treat Options Oncol. 2000;1(2):147–55.

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