Cervical Cancer, an Emerging Health Burden for Womenhood

Shubham Lingappanoor1*, Vasthalya Meesala1, Geetha Rani Manupati1, Padma Yaragani2, Brahmani Bachu3, Shyam Sunder Anchuri3
1Pharm-D Intern, Department of Pharmacy Practice, Balaji Institute of Pharmaceutical Sciences, Laknepally, Narsampet, Warangal
2Department of Obstetrics and Gynecology, CKMGMH, Kakatiya Medical College, Warangal-506002
3Department of Pharmacy Practice, Balaji Institute of Pharmaceutical Sciences, Narsampet, Warangal, Telangana State, India-506331

*Corresponding Author:
Shubham Lingappanoor
Pharm-D Intern, Department of Pharmacy Practice
Balaji Institute of Pharmaceutical Sciences, Laknepally, Narsampet, Warangal, Telangana State, India-506331

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ABSTRACT
Cervical cancer is the most common cause of deaths in women worldwide and is the second most cancer in women of reproductive age after breast cancer. The cervical cancer burden is over 18 times greater in low- and middle-income countries (LMICs) than in high-income countries. 15 genotypes of the Human Papilloma Virus found to cause cervical cancer and are transmitted sexually. Persistent infection with high-risk viral types, a large number of lifetime sexual partners, co-infection with human immunodeficiency virus, immunosuppression and cigarette smoking are the risk factors for tumor development. HPV-induced carcinoma of the cervix can develop within 2 years after initial infection or may develop cancers from or adjacent to precursor lesions that progress from one stage to another over 10–30 years. Cervical cancer is a curable and preventable disease. The earliest stages of cervical cancer can be treated with surgery or radiation combined with chemotherapy and the later stages are treated with radiation combined with chemotherapy. Use of barriers in sexual intercourse, prophylactic vaccination against persistent HPV infection can prevent the cervical cancer.

Keywords: Cervical cancer, Chemotherapy, Curable, Human Papilloma Virus, Preventable, Radiotherapy, Vaccination.

INTRODUCTION
Cervical cancer is the third most common cancer in women, a major public health burden to women in many low and meddle income countries [1]. Cervical cancer is the most common cause of cancer related death in women, and it is the second most common cancer after the breast cancer worldwide, and is the second leading malignancy in women aged 15–44 years of developing countries like India [2-4]. It is estimated that 528,000 new cases and 266,000 deaths among women each year are due to cervical cancer. A disproportionate number of these cases (85 %) and deaths (87 %) occur among women living in low and middle income countries [5]. India accounts for one-third of the cervical cancer deaths globally. In absolute terms, there are over 130,000 new cases of cervical cancer every year and nearly 74,000 deaths, according to this “per every 7 minutes, Indian women are dying due to cervical cancer” [6]. Cervical cancer is preventable and curable, if detected early or in pre-invasive stages [7].
Human papilloma virus (HPV) is the causative organism in almost all the cases, approximately 15 carcinogenic HPV genotypes are identified as the essential cause of cervical cancer [8, 9]. The natural history of HPV infection leading to invasive cancer is summarized by 4 measured stages: HPV acquisition, HPV persistence (V/s. clearance), progression of a persistent infection to cervical pre-cancer, and invasion [10]. Cervical cancer is a multi-etiologic disease, and HPV infection alone is not a sufficient cause of cervical cancer. Most HPV infections regress rapidly without causing clinically significant disease [11, 12]. Cofactors such as low socioeconomic status, tobacco, smoking, sexual and reproductive factors, HIV and other sexually transmitted diseases, long-term oral contraceptive use, certain micronutrient deficiencies and genetic susceptibility have been suggested as determinants [13, 14].

The cervical cancer burden is over 18 times greater in low- and middle-income countries (LMICs) than in high-income countries, having ill-equipped health systems where prevention, screening and treatment are limited in both availability and accessibility [15-20]. Early cervical cancer is often asymptomatic while locally advanced disease could cause symptoms including abnormal vaginal bleeding, also after coitus, discharge, pelvic pain, and dyspareunia. Squamous cell carcinoma, adenocarcinoma and adenosquamous carcinoma are the three major histological types, and this cancer develops slowly and locally. Depending on the type stage of cancer, more than one type of treatment may be used in combination. For the earliest stages of cervical cancer, surgery or radiation combined with chemotherapy are used. Later stages are treated with radiation combined with chemotherapy [21, 22].

Epithelial tumors of the cervix: squamous, glandular (adenocarcinoma) and adenosquamous carcinoma are the three major histological types, and this cancer develops slowly and locally [23]. Prophylactic HPV vaccination, use barriers in intercourse and regular screening tests are important strategies to prevent cervical cancer [24].

**ETIOLOGY**

Almost all (99.7%) cervical cancer cases are result of persistent infection with high risk type HPV [8]. More than 100 different types of the virus exist, including approximately 30 to 40 strains that infect the human genital tract. Of these, there are oncogenic or high-risk types such as 16, 18, 31, 33, 35, 39, 45, 51, 52, and 58 that are associated with cervical, vulvar, vaginal, and anal cancers, and non-oncogenic or low-risk types are 6, 11, 40, 42, 43, 44, and 54, associated with genital warts [9].

A higher incidence of HPV infection and progression of intraepithelial neoplasia is seen in immunosuppressed patients, including those infected with HIV as well as those who are organ transplant recipients, who have chronic renal failure or a history of Hodgkin lymphoma, or have undergone immunosuppressive therapy for other reasons, women with large number of sexual partners and cigarette smoking. First intercourse at a young age may increase a woman’s risk for cervical neoplasia because of the high rate of metaplasia that occurs in the transformation zone during adolescence and a higher proportion of new or immature cervical cells in this region [25, 12, 13, 26].

**PATHOPHYSIOLOGY**

Virtually all cervical cancers are sexually transmitted diseases, caused by carcinogenic HPVs that are unimpeded by barrier contraceptives and infect unstable (metaplastic) cervical squamous epithelium of the transformation zone [27, 28]. Young women have large areas of immature metaplastic cervical epithelium, which appear to be the most susceptible of all squamous epithelia to infection by carcinogenic HPV. If sexual activity begins at an early age, especially with multiple partners harboring carcinogenic HPV, the women are at high risk for developing cervical neoplasia [27, 29, 30].

At puberty, in pregnancy (particularly the first one), and in some steroid contraceptive users, changes in the size and shape of the cervix result in the squamocolumnar junction being carried out on to the anatomical ectocervix. This exposes the tissues previously found in the lower endocervical canal to the vagina. This is a physiological process and the exposed tissue forms the “cervical ectopy”. Under physiological conditions, the columnar epithelium of the ectopy undergoes metaplasia to a stratified squamous epithelium, and it is during this metaplastic process that the epithelium seems to be particularly vulnerable to oncogenic viruses, and perhaps to other factors resulting in the development of an
intraepithelial neoplasm rather than a normal epithelium. The intraepithelial neoplasm may be of squamous or columnar cell type [31].

Most invasive carcinomas of the cervix develop from an intraepithelial neoplasm that has formed in the tissues of the cervical ectopy [32, 33]. They tend to lie, therefore, on the ectocervix in younger women and in the endocervical canal in older woman (see above). The tumors may have an exophytic or endophytic pattern of growth, those on the ectocervix being more commonly exophytic and those in the endocervical canal more commonly endophytic. This has clinical importance in that exophytic tumours on the ectocervix are less likely to have extended into the adjacent tissues and organs than endophytic tumours of similar size, and are less likely to have metastasized [34, 35].

HPV-induced carcinoma of the cervix can develop within 2 years after initial infection of unstable squamous epithelia of endocervix; however, most cancers develop from or adjacent to precursor lesions that progress from one stage to another over 10–30 years. Over time, uninfected metaplastic squamous epithelium matures and appears to become more susceptible to no-risk or low-risk viruses such as HPV-6 that have a tropism for mature squamous epithelium of the mucosal surfaces [36].

The presence of abnormal precancerous cells in Pap smear test is termed Cervical Interepithelial Neoplasia (CIN) or Squamous Intraepithelial Lesions (SIL). If not early detected or not properly treated this cervical dysplasia can further develop to an invasive carcinoma. The progression CIN is divided into three stages: CIN 1, CIN 2 and CIN 3 (Figure 1) [37, 38].

**Figure 1:** Progression of Cervical Intraepithelial Neoplasia (CIN) in the squamous epithelium of cervix

Figure 1, shows a schematic interpretation of the progress from normal cervical epithelium, through the precancerous stages known as cervical intraepithelial neoplasia (CIN), or alternatively squamous intraepithelial lesions (SIL) to overt cervical carcinoma. The changes include an increased nuclear–cytoplasmic ratio, loss of the layer of flattened cells close to the surface and an increase in the volume of extra-cellular space [39, 40]. Clearance of the HPV infection is often rapid, with more than half of infections clearing (undetectable using standard DNA/RNA detection methods) within a year, and 90% of infections within approximately 2 years of acquisition. The carcinomas can invade locally into the cervical stroma, the paracervical and parametrial tissues, the body of the uterus, the vagina, and, late in the course of the disease, to the bladder and rectum and it may spreads to the distant organs such as liver, lungs, bones and bowel [41-43].
Table 1: TNM and FIGO staging system for cervical cancer

<table>
<thead>
<tr>
<th>TNM stage</th>
<th>FIGO stage</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td></td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>I</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>0</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1</td>
<td>I</td>
<td>Tumor confined to the uterus (extension into the corpus should be disregarded)</td>
</tr>
<tr>
<td>T1A1</td>
<td>IA1</td>
<td>Minimal microscopic stromal invasion</td>
</tr>
<tr>
<td>T1A2</td>
<td>IA2</td>
<td>Invasive component 5 mm in depth and 7 mm in horizontal spread</td>
</tr>
<tr>
<td>T1B</td>
<td>IB</td>
<td>Invasive component larger than in T1A2</td>
</tr>
<tr>
<td>T2</td>
<td>II</td>
<td>Tumor extends beyond the uterus but not to the pelvic wall or the lower one-third of the vagina (can involve the proximal vagina)</td>
</tr>
<tr>
<td>T2A</td>
<td>IIA</td>
<td>No parametrial invasion</td>
</tr>
<tr>
<td>T2B</td>
<td>IIB</td>
<td>Parametrial invasion</td>
</tr>
<tr>
<td>T3</td>
<td>III</td>
<td>Tumor extends to the pelvic wall, involves the lower one-third of the vagina, or causes hydronephrosis or a non-functioning kidney</td>
</tr>
<tr>
<td>T3A</td>
<td>IIIA</td>
<td>Tumor involves the lower one-third of the vagina but does not extend to the pelvic wall</td>
</tr>
<tr>
<td>T3B</td>
<td>IIIB</td>
<td>Tumor extends to the pelvic wall or causes hydronephrosis or a non-functioning kidney</td>
</tr>
<tr>
<td>T4</td>
<td>IVA</td>
<td>Tumor involves the mucosa of the bladder or rectum or extends beyond the true pelvis</td>
</tr>
<tr>
<td>MX</td>
<td></td>
<td>Distant metastases cannot be assessed</td>
</tr>
<tr>
<td>M0</td>
<td></td>
<td>No distant metastases</td>
</tr>
<tr>
<td>M1</td>
<td>IVB</td>
<td>Distant metastases</td>
</tr>
<tr>
<td>NX</td>
<td></td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td></td>
<td>No regional lymph node metastases</td>
</tr>
<tr>
<td>N1</td>
<td></td>
<td>Regional lymph node metastases [44].</td>
</tr>
</tbody>
</table>

SCREENING

Physical examination should include general examination and an abdominal and pelvic examination. This enables any pelvic masses to be palpated, and vaginal mucosa, cervical discharge, uterine size, masses, adnexal masses and polyps/carcinoma are observed [45, 46].

PAP smear is a simple, safe, non invasive and effective cytological test designed to detect abnormal cervical cells from cervical transformation zone the purpose of Pap smear or any screening modality is to divide population into those who are likely to harbor the disease and those who are not [47]. Visual inspection with acetic acid (VIA) Visual Inspection with Lugol’s Iodine (VILI) is considered as an attractive alternative to cytology-based screening in low-resource settings, include low cost, simple administration, real time screening, of results, and accuracy comparable to good quality Pap smears [48, 49].

A colposcopy uses a low-power, stereoscopic, binocular field microscope containing a powerful light source, used for magnified visual examination of the uterine cervix to help in the diagnosis of cervical neoplasia. The most common indication of referral for colposcopy is positive screening tests (e.g., positive cytology, positive on VIA) [50].
Biopsy and histopathologic evidence of invasive malignancy should precede any treatment modality. This may be from a suspicious growth, edge of an ulcer or colposcopy-directed biopsy from suspicious areas, with an amplified visual assessment of the cervix supported by utilizing weaken acidic corrosive (e.g. vinegar) answer for highlight irregular cells on the surface of the cervix. Therapeutic gadgets utilized for biopsy of the cervix incorporate punch forceps, SpiraBrush CX, Soft Biopsy, or Soft-ECC [51, 52].

The causal HPV strains are detected by HPV-DNA testing, where the most widely used, commercially available method is HC2 (Digene, Gaithersburg, Maryland, USA). This test uses two separate probe mixtures to identify either low risk types of HPV (6, 11, 42, 43 and 44) or high risk types of HPV (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68) [53, 54]. Cervical biomarkers currently under study include proliferation markers (PCNA), regulation markers (growth factor receptors, ras, myc, p53, retinoic acid receptors, spermidine/spermine ratios), differentiation markers (involutulin, cornifin, keratins), and markers of genetic instability (chromosome polysomy) [55].

Two automated screening systems have been FDA-approved for use: AutoPap System (Neopath, Inc. Redmond, VA) and PapNet (PapNet, NetMed Inc., Columbus, OH). AutoPap, which reviews negative smears and selects a population at increased risk for abnormalities, was initially approved for quality control re-screening and most recently for primary screening. PapNet, on the other hand, is designed as an adjunct to manual screening by selecting the most abnormal 128 images on a slide for review [56, 57].

Sonography can play an invaluable role in the primary diagnosis of gynecological cancers, the assessment of tumor extent in the pelvic and abdominal cavity and the evaluation of treatment effects as well as follow-up after treatment. Using ultrasound to evaluate important prognostic parameters makes the individualization of oncology treatment possible [58]. Cross-sectional imaging (CT, MRI, PET-CT) provides more accurate evaluation of local and extrauterine cervical cancer spread and, at the same time, limits the cost of staging. Although the last revision of FIGO staging criteria recommends inclusion of these imaging techniques when possible, their use remains optional [59].

**MANAGEMENT**

![Flow chart showing management options available with suspicion of cervical cancer incorporating minimal access surgery](image-url)

**Figure 2:** Flow chart showing management options available with suspicion of cervical cancer incorporating minimal access surgery
The management options to be considered include surgery, radiotherapy, chemotherapy and combinations of these modalities (Fig. 2). Age in itself is not a barrier to full assessment and definitive treatment. The women should be divided into those in whom the treatment is curative or palliative. For those with early stage cervical cancer curative intent with surgery or radiotherapy needs to be contemplated. In those with more advanced disease, chemoradiotherapy is the optimal method of management but surgery may have a role in a palliative setting [2].

For stage 0 to IB1 cancers and for some stage IIA cancers, the treatment may include surgery, radiation therapy, or both, depending on patient and physician preference. Bulky stage I (stage IB2) and locally advanced (stages II-IVA) cervical cancers are treated with concurrent chemoradiation in the United States. Palliation with platinum based chemotherapy remains the standard of care for inoperable patients who have advanced disease [60].

The treatment options for cervical cancer bases on stage of the disease, as follows (Table 1):

**Stage 0:** Carcinoma in situ (stage 0) is treated with local ablative or excisional measures such as cryosurgery, laser ablation, and loop excision; surgical removal is preferred

**Stage IA1:** The treatment of choice for stage IA1 disease is surgery; total hysterectomy, radical hysterectomy, and conization are accepted procedures

**Stage IA2, IB, or IIA:** Combined external beam radiation with brachytherapy and radical hysterectomy with bilateral pelvic lymphadenectomy for patients with stage IB or IIA disease; radical vaginal trachelectomy with pelvic lymph node dissection is appropriate for fertility preservation in women with stage IA2 disease and those with stage IB1 disease whose lesions are 2 cm or smaller

**Stage IIB, III, or IVA:** Cisplatin-based chemotherapy with radiation is the standard of care

Stage IVB and recurrent cancer: Individualized therapy is used on a palliative basis; radiation therapy is used alone for control of bleeding and pain; systemic chemotherapy is used for disseminated disease [61].

For patients with locally recurrent cervical cancer radiation therapy is indicated, following radical surgery. Concurrent chemotherapy with either fluorouracil and/or cisplatin with radiation should be considered and may improve outcome [62]. A number of targeted and immunotherapeutic agents are in clinical use or in phase II/III studies in cervical cancer. Few of them are VEGF/VEGFR inhibitors like Bevacizumab, pazopanib, sunitinib, nintedanib, brivanib, cediranib, Immune checkpoint inhibitors like Pembrolizumab, Ipilimumab and Nivolumab etc [63]. The survival rate is close to 100%, when precancerous or early cancerous changes are found and treated [64].

**PREVENTION**

As primary prevention, use of condoms and Prophylactic vaccination against persistent HPV infection offers an alternative preventive strategy against cervical cancer particularly in developing countries which lack a nationally organized cervical screening program [24, 65]. The WHO recommends the inclusion of HPV vaccination in national immunization programs provided HPV represents a public health priority and vaccine delivery is feasible and cost-effective [66].

The HPV vaccines currently available are—the bivalent vaccine (Cervarix, Glaxo SmithKline Biologicals) and the quadrivalent vaccine (Gardasil, Merck). These vaccines aim to prevent infection from HPV types 16 and 18, since these two types are most carcinogenic and are responsible for majority of cervical cancers. The risk of developing squamous cell carcinoma of cervix is 435 times higher if someone is infected by the HPV 18 and 248 times higher if someone is infected by the HPV 16, compared to non-infected individuals [9].

However, barriers to vaccination such as, concerns about the safety of the vaccine, provider reservations about recommending vaccination for younger girls, limited awareness of the relationship between HPV and cervical cancer, and varied parental acceptance of the HPV vaccine resulting in non or low uptake of vaccination [67-70].

The challenges and failure in implementing cervical cytology screening in resources poor settings has resulted into exploring alternative methods for down staging of the cervical cancer during last decade.
Some of these methods such as visual inspection of cervix with acetic acid (VIA), visual inspection of cervix with lugol’s iodine (VILI), use of magnascope instead of colposcope, single visit approach, treatment with cryosurgery for via +ve women, self collected samples for cytology and Human Papilloma Virus (HPV)-DNA testing, education and counseling, increasing coverage by camp approach, low cost HPV tests and providing HPV vaccines [71].

CONCLUSION

Though, the cervical cancer is a curable and preventable disease, the lack of knowledge about the disease and preventive measures among the women of reproductive age and girls of teenage leading to the growing burden of the cervical cancer in developing countries. The treatment and preventive measures are remaining unreached for the women of rural areas. The awareness campaigns on health education and appropriate, accessible and effective methods to prevent the HPV infection and screen and treat methods like Visual examination and easy to implement tests like VIA/VILI helps in reduction of subsequent progression of HPV infection to the cervical cancer are necessary overcome the current problem on cervical cancer.

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