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UNDERSTANDING HPV: THE LEADING CAUSE OF CERVICAL CANCER

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Abstract :

Human Papillomavirus (HPV) is widely recognized as the primary cause of cervical cancer which remains one of the leading causes of cancer-related deaths among women worldwide. This abstract explores the virology, epidemiology, and pathogenesis of HPV, focusing on how it initiates cellular changes that lead to cervical cancer. HPV is a highly prevalent sexually transmitted infection, with over 200 types identified, of which approximately 14 are high-risk types associated with cancer, particularly HPV-16 and HPV-18. Persistent infection with these high-risk types is necessary for the progression from cervical intraepithelial neoplasia (CIN) to invasive carcinoma. The virus interferes with tumor suppressor pathways, primarily through the actions of E6 and E7 viral oncoproteins, which inactivate p53 and retinoblastoma protein respectively, allowing for unchecked cellular proliferation. Screening programs, including Pap tests and HPV DNA testing, have significantly reduced the incidence of cervical cancer by detecting precancerous lesions early. Vaccines against HPV, notably the quadrivalent and nonavalent vaccines, have shown high efficacy in preventing infection with the most dangerous HPV types. Despite these advances, challenges remain, particularly in low-resource settings, where access to vaccines and screening is limited. Comprehensive prevention strategies that combine vaccination, regular screening, and public education are essential to reduce the global burden of cervical cancer.

Keywords : Human Papillomavirus (HPV) Chemotherapy Pregnancy & Cervical Cancer: Cervical Cancer: Primary Radiation Therapy:

Introduction:

Eighty-three women, with a mean age of forty-five, who underwent successful surgery (S) or radiation therapy (RT) for stage III cervical cancer were evaluated an average of 97 weeks after treatment. Weight increase, insufficient energy, and chronic fatigue were noted by 40–50% of respondents. 60% had not returned to their pre-morbid level of functioning. Of those who would have preferred counselling, 49% said they would have. By focussing more on these women's psychological and sexual problems, their functional, emotional, and sexual status might be improved even though they had the same physical morbidity. Globally, cervical cancer (CC) continues to be a major source of morbidity and mortality. Dangerous human papillomavirus (HPV) infection must continue for the onset of CC.(1)

The HPV vaccination serves as primary prevention, while population-based screening serves as secondary prevention. The aforementioned disparities in rates between high- and low-income nations are primarily the result of these preventative interventions' efficacy. In high-income nations, vaccination rates are high and the DNA-HPV test is a useful screening tool. In low-income countries, vaccination rates are low and screening is based on opportunistic cervical cytology programs. The DNA-HPV test is recommended as the most effective primary screening method by the American Cancer Society, the Society of Gynaecologic Oncology, and the European Guidelines for Quality Assurance in Cervical Cancer Screening. With about 500.000 new cases annually, cervical carcinoma is the most common gynaecological malignancy globally and is especially common in underdeveloped nation . In developed nations, it is the tenth most prevalent cancer to affect women. There has been a rise in the number of young women diagnosed with cervical cancer in recent years. A growing percentage of women with cervical cancer are receiving early diagnosis thanks to the efficient use of screening.(2)

Women with uterine-confined cervical cancer are in the early stages of the illness. A major health concern, cervical cancer affects around 500 000 women globally each year. Human papillomavirus exposure, smoking, and immune system dysfunction are risk factors. most females with tumour in their early stages can be treated, while treatment related longterm morbidity is typical. The standard of care for women with locally advanced tumours should be chemoradiotherapy, according to the results of randomised clinical studies. However, there is still much to be learnt about how well this treatment works for women in less developed nations. Even today, many women with localised (stage IB) cancers receive different regimens of radiation and surgery, despite unanswered questions regarding the approach's higher morbidity when compared to definitive treatment.(3)

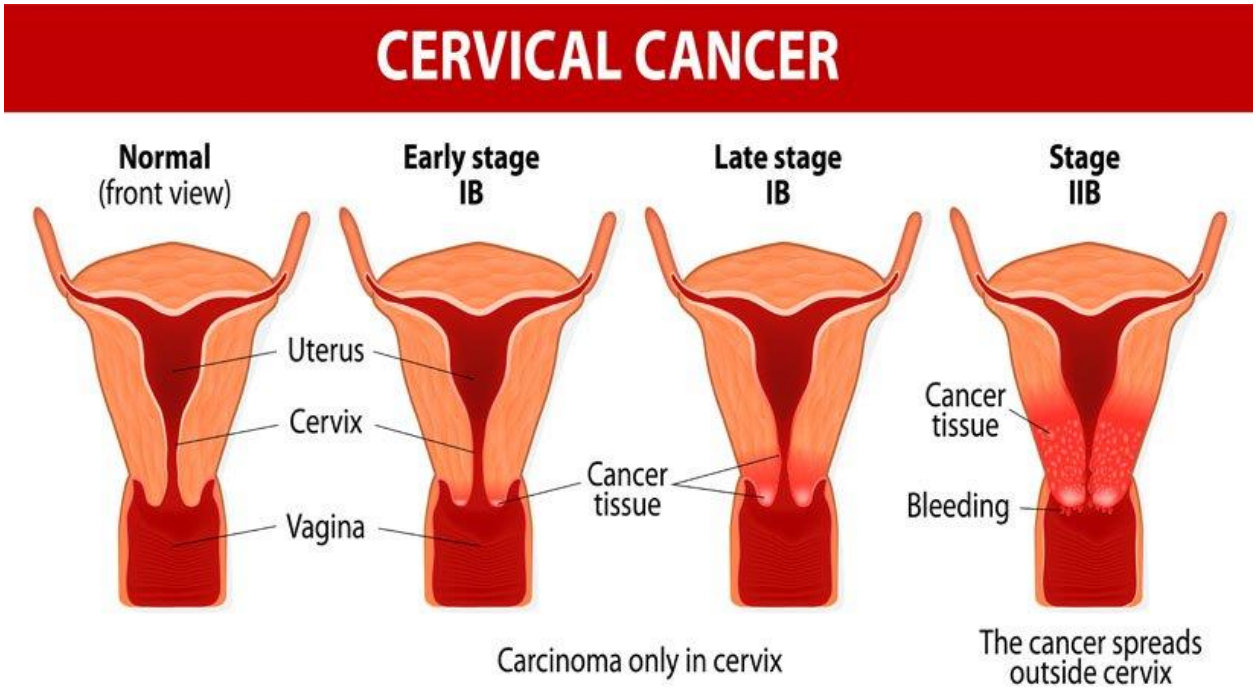

Fig 1: Cervical cancer(4)

Cervical Cancer:

A cancerous tumour of the cervix is the base of the uterus. A cancerous tumour of the lowest portion of the uterus (womb) that is preventable with an HPV vaccination and PAP smear screening. Bleeding during and after menstruation are among the symptoms. There may also be a foul-smelling white discharge, lower back pain, or lower stomach pain. Sometimes there won't be any symptoms at all.(5)

Epidemiology and risk factors:

With almost 80% of occurrences occurring in less developed nations, cervical cancer is the second most frequent malignant disease among women worldwide. According to predictions from the American Cancer Society, 4100 women will pass away from cervical cancer in 2002, out of an estimated 13,000 cases that were identified in American women. Almost half of cases are diagnosed before the age of 35 in North America, where the median age upon diagnosis is 47. However, due mostly to more advanced illness at diagnosis, women over the age of 55 contribute disproportionately to the mortality rate from cervical cancer. The human papillomavirus is the main cause of cervical cancer (HPV). HPV DNA can be found in more than 90% of squamous cervical malignancies. The majority of invasive malignancies are caused by HPV types 16, 18, 31, 35, 39, 45, 51, 52, 56, and 58, despite the fact that many of these kinds have been linked to anogenital neoplasia.7. HPV-16 and 18 possess two transcriptional units, E6 and E7, which code for proteins necessary for the reproduction of the virus. The E6

oncoprotein breaks an innate cell-cycle checkpoint by binding to and inactivating the tumour-suppressor gene TP53 via ubiquitin degradation.(6)

Staging:

STAGE I A:

Microinvasive or stage IA cervical cancers are frequently found in women with Papsmear test positive in many more developed nations with well-established screening programs are asymptomatic and upon gross examination, appear to have normal cervices. Although many cases of superficially invasive cervical cancer are unintentionally found after hysterectomy, the diagnosis is typically made following a cervical conisation. Less than 1% of cases include pelvic nodes if the invasion focus reaches no deeper than 3 mm below the basement membrane (stage IA1). Patients who wish to maintain their fertility may find cervical conization to be an acceptable therapy option. The existence of a lymphatic or vascular space invasion, according to FIGO, should not alter the stage but instead noticed by the pathologist, since concerns over the potential of nodal involvement may impact therapy recommendations (see below). The preferred course of treatment for patients who have finished having children is still extrafacial hysterectomy, either via abdominal or vaginal means. During a pelvic lymphadenectomy, lymph nodes from the obturator, common, external, and internal iliac areas are removed. The paraaortic Unless there are worrisome pelvic lymph nodes found, lymph node dissection is not required.

When there is an invasion of the lymphatic or vascular area, the optimal course of treatment for microinvasive squamous-cell carcinoma is still unclear. assault on the lymphatic system or vascular space has been linked to a higher incidence of metastases from pelvic lymph nodes. As a result, the majority of gynaecological oncologists recommend radiation therapy or a total hysterectomy along with pelvic lymphadenectomy. Microinvasive adenocarcinoma lacks a defined classification, mostly due to the challenge of recognising the basement membrane in the endocervical region and the occurrence of "skip lesions" in hysterectomy specimens taken subsequent to a conization. However, mounting data indicates that, for adenocarcinomas penetrating less than 3 mm, pelvic lymph-node metastasis is extremely rare, even when precise tumour measurements are achievable. Although research comparing the kind (radical or extrafascial) and route (vaginal or abdominal) of hysterectomy are scarce, hysterectomy is still considered the standard of care. For Conservative treatment with close monitoring has been utilised for patients who wish to maintain their fertility and who show minimal stromal invasion on a conisation specimen and negative margins for invasive or in-situ lesions. The patient needs to be informed of the drawbacks of this course of treatment, such as the possibility of cancer returning.(7)

Stage IB:

Morbidities associated with radical hysterectomy include chronic bladder dysfunction (3%), ureterovaginal or vesicovaginal fistula (1-2%), pulmonary embolism (1-2%), smallbowel obstruction (1%), lymphocoele formation (5%), nerve (obturator, genitofemoral) injury, and the risks associated with blood loss requiring transfusion. Some researchers have advocated use of a modified radical hysterectomy for the treatment of small cervical lesions in order to limit some of the morbidity associated with a more radical procedure.

When treating stage IB cervical cancer, factors such as the tumor's size, the patient's age, the presence of comorbidities, and the treatment facility's resources should all be taken into account. In 1994, FIGO substratified stage IB cancers into those with a diameter of less than and more than 4 cm (stages IB1 and IB2) in order to reflect the higher recurrence rate and danger of nodal dissemination by the larger tumours. Treatment options for stage IB1 tumours include primary radiation or total hysterectomy along with pelvic and paraaortic lymphadenectomy, which is usually effective. Several risk variables for recurrence were found in a prospective surgical pathology analysis of individuals treated with radical hysterectomy for stage IB cervical cancer big tumour diameter, severe cervical stromal infiltration, and lymphatic or capillary space tumour presence. After surgery, an estimation of the probability of recurrence could be obtained by taking these parameters into account. GOG conducted a prospective trial based on these pathological features, randomly assigning patients with varying combinations of these risk factors to adjuvant pelvic radiation or no further therapy at all. The majority of patients had tumours larger than 3 cm in diameter that either deeply invaded the cervical stroma or involved the capillary-lymphatic space. Patients with affected vaginal or parametrial margins, or those with positive lymph nodes, were not eligible for the experiment. For stage I cervical cancer, primary radiation therapy has cure rates that are comparable to those of radical hysterectomy.Traditional radiation therapy consists of a mix of both intracavitary brachytherapy and external radiation are used. The primary targets of wholepelvis radiation therapy, which usually ranges from 40 to 50 Gy, are the lateral pelvic walls, including the pelvic lymph nodes, and the parametrial tissue. Treatment is given in daily fractions over a period of 4-5 weeks. Because external irradiation reduces the bulk of the central tumour and enables more effective dosimetry in brachytherapy application, it usually comes before brachytherapy. Brachytherapy can be administered at a low or high dose rate, with comparable outcomes.
Low-dose-rate therapy (4–20 Gy/h) usually requires a two–three day hospital stay in addition to the brachytherapy implant device being placed under anaesthesia.(8-9)

Stage IIA:

Depending on the degree of cervical and vaginal involvement, each patient's course of treatment should be customised. Most individuals with stage IIA cancers ought to undergo chemotherapy and radiation treatment. Rarely, the cancer can be successfully treated with radical hysterectomy, lymphadenectomy, and upper vaginectomy if there is not much cancerous extension into the vaginal fornix.(10)

Stages IIB, III, and IVA:

If cervical cancer has progressed outside of the cervix, intensive surgery probably won't be enough to cure it. The results of several randomised clinical trials showed that patients having chemoradiotherapy had better survival and a shorter time to progression than receiving radiation therapy alone. The National Cancer Institute states that concurrent chemotherapy and radiation therapy need to be considered standard care for high-risk early-stage cervical cancer or locally advanced (stage IIB–IVA) cervical cancer. Each of these clinical trials had cisplatin as part of the therapy regimen, occasionally in addition to fluorouracil. Nevertheless, a GOG trial found that a weekly regimen consisting of cisplatin, fluorouracil, and hydroxyurea was equally effective and less harmful than the combination of these three medications. Cisplatin once a week is an easy regimen to stick to chemoradiotherapy was generally shown to be more effective than either radiotherapy alone or radiotherapy following neoadjuvant chemotherapy, according to a systematic review and metaanalysis of data on the subject. That review indicated that the combination of radiation therapy and chemotherapy improved overall survival by over thirty percent and reduced the risk of both local and distant recurrence. Although bigger survival benefits have been discovered in other studies, the anticipated absolute survival benefit was 12%. Significant problems remain unanswered and it has not been demonstrated that chemotherapy is a necessary adjunct for all patients receiving primary or adjuvant radiotherapy.(11)
For example, it is not known if women whose cancer has advanced to the para-aortic lymph nodes may benefit from chemotherapy or radiation therapy. Similarly, chemoradiotherapy is being given to a substantial number of women with stage IB tumours who have intermediate risk factors for recurrence after radical hysterectomy, despite the absence of evidence of benefit in a randomised clinical study. Such a study would require substantial resources and could take ten years or longer to complete. Patients undergoing chemotherapy and radiation treatment often experience more severe toxic effects on the gastrointestinal tract and haematological system, which could impose a pressure on resources in developing countries. Although cisplatin is the drug of choice, not enough study has been done on its use when radiation therapy is administered to women whose renal function is only slightly affected. Whether using less nephrotoxic, alternative drugs can improve the survival rate of this patient subgroup.(12-13)

Diagnosis and pathology:

When a lesion on the cervix is visible or a Pap smear is analysed, cervical cancer may be suspected. Any worrisome lesion has to have a biopsy sample collected because in the presence of aggressive cancer, a large number of Pap smears are either non-diagnostic or erroneously negative. A cone biopsy should be performed if the biopsy sample reveals cells that may indicate microinvasion and the patient does not have an invasive malignancy that is visibly noticeable. It is necessary to extract enough underlying stroma to enable a proper assessment of the depth and width of penetration below the basement membrane in order to accurately stage clinically occult lesions. Cervical adenocarcinoma represents around 20% of invasive cervical cancer cases.(15-16)

Malignancies; in industrialised nations, adenocarcinoma incidence is increasing relative to squamous cancer incidence. Smoking does not appear to be a risk factor for adenocarcinomas, despite the fact that oncogenic HPV DNA has been found in these histological subtypes. Adenocarcinoma-in-situ is most likely the precursor lesion in most cases, however Papsmear screening detects it considerably less well than preinvasive squamous lesions. Less than 5% of adenocarcinomas are clear-cell carcinomas, a rare form of the disease.(17-18)

Physical examination:

Palpation of lymph nodes.

Vaginal examination.

Rectovaginal examination with or without anaesthesia.

Radiographic studies:

Chest radiograph.

Skeletal radiograph.

Intravenous pyelogram.

Barium enema.

Procedures:.

Cervical biopsy.

Cervical conisation.

Hysteroscopy.

Colposcopy.

Endocervical curettage.

Cystoscopy.

Proctoscopy.

Other studies:

Computed tomography.

Magnetic resonance imaging.

Positron emission tomography with fluorodeoxyglucose.

Ultrasonography.

Bone scanning.

Lymphangiography.

Laparoscopy.(19-22)

Treatment:

Chemotherapy:

Chemotherapy has always been seen as palliative when used for advanced or recurring disease. Numerous agents have been studied in alone or in combination with other agents.In multicenter phase-2 trials, responder rates typically range from 10% to 40%; full responses are observed infrequently and for brief periods of time. Currently, cisplatin is thought to be the most effective single treatment for recurrent illness. The combined treatment resulted in reversible bone-marrow toxic effects but was superior to single-agent cisplatin in terms of response rate and survival. There is not yet a published quality-of-life assessment for either of the two therapy groups, and the survival benefit is only a few weeks. If a recurrence takes place in an area that has already been exposed to radiation, this appears to have a negative impact on the efficacy of chemotherapy. Chemotherapy is effective for about 25% of patients whose recurrence occurs outside the irradiated zone, whereas only 5% of patients whose recurrence occurs inside the irradiation field. Whether combined chemotherapy can improve distant control over the long term by acting as a radiation sensitiser. This phase 3 experiment aims to investigate the possible advantages of aggressively correcting anaemia following radiation therapy. Additional research focusses on ways to enhance radiation and surgery methods to reduce morbidity and enhance the quality of existence. For many women treated for cervical cancer, radiation therapy and major surgery especially when administered in combination are linked to severe, long-term morbidity.(23-26)

Primary Radiation Therapy:

For women who are not candidates for surgery because of medical comorbidities or poor functional status, RT is reserved as the initial course of treatment. While some professionals would rather combine RT combined with chemotherapy (concomitant chemoradiation) in these patients; nevertheless, there is little information to support the advantages of chemotherapy in order to mitigate treatment morbidity in females with early-stage cervical cancer.

Adequate coverage of the cervix, rectum, bladder, small bowel, and nodal sites is achieved with the use of CT-based planning. Radiation field bounds in typical 2D are relative to skeletal anatomy. A sufficient amount of soft tissue regions at risk, such as the pelvic lymph nodes and the surrounding vaginal and parametrial tissue, are covered by 3D conformal radiotherapy. When planning radiation therapy, MRI and PET scans can be used to assess the size and location of the primary tumour as well as the degree of bladder or rectal invasion, parametrial involvement, and nodal illness The fourfield approach has been used to administer treatment in the past. Usually, 45 Gy is administered to the whole pelvis in 25 once-daily fractions of 1.8 Gy. These areas are increased to 50.4 to 60 Gy using external beam radiation, frequently using a specially designed central block to protect the vagina and uterus, which will receive additional brachytherapy treatment.(27-30)

Locoregional Therapy:

After receiving first treatment, patients who experience a localised recurrence of cervical cancer should be assessed to see if surgery or radiation therapy can be utilised to treat the relapse. In certain circumstances, long-term disease-free survival rates of about 40% have been seen. For individuals with locoregional recurrences who have not had prior radiotherapy or who have recurrences outside of the previously treated RT field, platinum-based chemotherapy with (or without) brachytherapy and tumor-directed RT are the treatments for relapse; if practical, surgical resection may also be undertaken. Generally, 5-FU in combination with cisplatin or cisplatin alone is used in chemoradiation therapy for recurrence.

Pelvic exenteration, with or without intraoperative radiotherapy (IORT), should be assessed in patients with central pelvic recurrent illness following radiotherapy. Generally speaking, surgical mortality is 5% or less, and survival rates are close to 50%. Adequate rehabilitation programs addressing the psychological and sexual fallout after the operation, as well as restorative surgeries, are complementary measures to these drastic procedures.While exenteration is the most common surgical strategy for postradiation patients, carefully chosen patients with tiny central lesions (< 2 cm) may also benefit from radical hysterectomy or brachytherapy.(31-33)

Pregnancy & Cervical Cancer:

Cervical cancer is the most common type of cancer detected in pregnant women; nevertheless, most pregnant women with cervical cancer have stage I illness. Pregnancy-related invasive cervical carcinoma presents a clinical conundrum. Depending on their disease stage, women must make the tough choice to either start therapy right away or postpone it until foetal maturity is confirmed. Children born to women who postpone therapy until foetal maturity should be delivered via caesarean section. It has been claimed that women who are diagnosed

with cervical cancer during pregnancy and would like to carry on with their pregnancies should postpone cancer treatment until the foetus is fully developed.

For patients whose disease is still in its early stages, radiation therapy may not be preferred over radical hysterectomy and node dissection their ovaries. Patients can have a caesarean section with radical hysterectomy and pelvic node dissection if they have early-stage illness and wait to receive therapy until the foetus is mature. Traditional RT with (or without) chemotherapy procedures (already outlined) may need to be adjusted for patients who elect to receive radiation therapy.(34-36)

Conclusion:

Cervical cancer deaths are decreasing in the United States due to widespread screening, but they are increasing in developing countries because many women lack access to screening. Surgery combined with concurrent chemoradiation can cure 80% of women with early-stage cervical cancer (stages I–II) and 60% of women with stage III sickness. In order to prevent women from developing specific HPV cancers, it is thought that using the new vaccines to immunise against HPV may prevent persistent infection with particular viral strains. Because screening is so widely used, the number of fatalities from cervical cancer is declining in the United States, but rising in developing nations, as many women do not have access to screening. Women with cervical cancer at all stages have benefited from enormous advancements in the disease's treatment over the last ten years. These developments, however, have not reached the great majority of women afflicted by the illness, who reside in underdeveloped nations with scant resources and no screening initiatives.

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