INTRODUCTION

Cervical cancer is a major world health problem for women and is the leading gynaecologic malignancy. [1]

Demographic Patterns

It is third most commonly diagnosed cancer in women and the fourth leading cause of cancer death in females worldwide.[2] It was accounting for 9% of the total new cancer cases and 8% of the total cancer deaths among females.[3] About 78 % of cases occur in developing countries and more than 85% of deaths occur also in developing countries where it is second most frequent cause of cancer death in women after breast cancer.[3,4]

The majority of women who develop cervical cancer are in their forties and fifties and more younger also women are being affected nowdays. It is no longer uncommon to see women in their twenties or thirties diagnosed with cervical cancer.[3]

Worldwide, the highest incidence rates are in Eastern, Western, and Southern Africa, as well as South-Central Asia and South America. Rates are lowest in Western Asia, Australia, New Zealand, and North America (Figure 1). The disproportionately high burden of cervical cancer in developing countries and elsewhere in medically underserved populations is largely due to a lack of screening that allows detection of precancerous and early stage cervical cancer.[3]

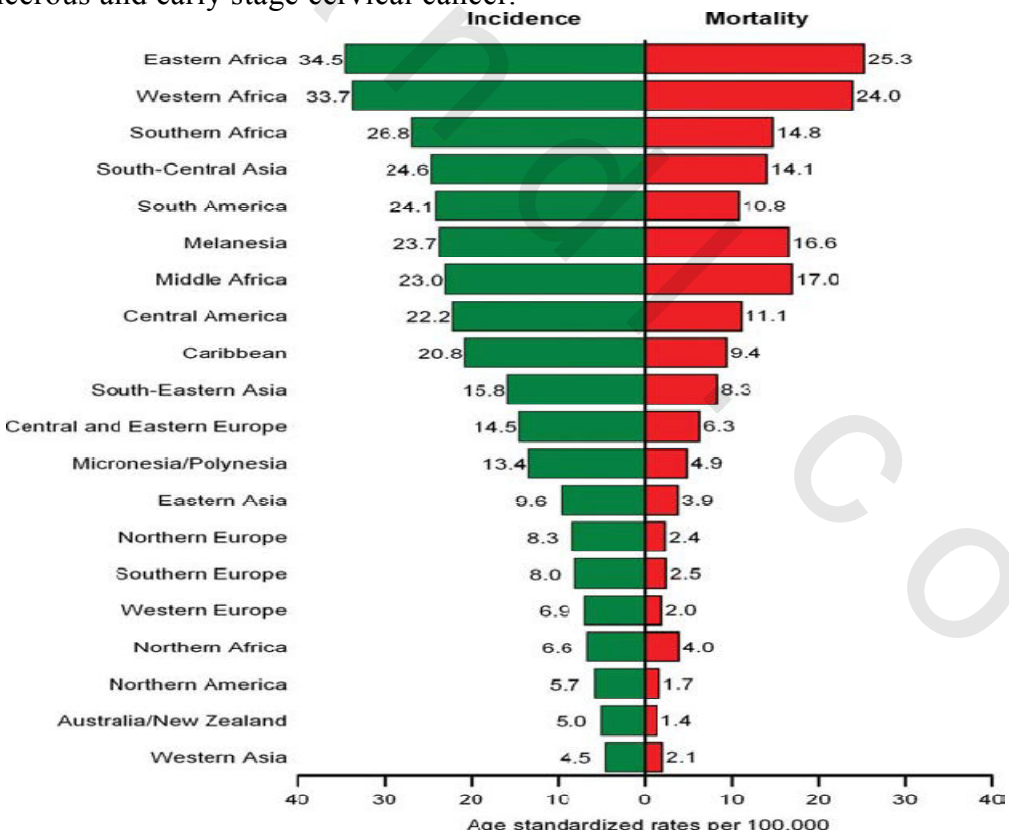

Figure (1): Age-Standardized Cervical Cancer Incidence and Mortality Rates by World Area. [2]

Anatomy:

The uterus is located in the central part of the pelvis between the bladder and rectum. It is divided into the corpus and cervix and is connected to the pelvis by the parametria and to the sacrum by the sacrouterine ligaments. The length of the uterine cavity varies somewhere between 4 and 10 cm. The diameter of the cervix varies between 2 and 5 cm, and its length varies between 2 and 5 cm (as the length of the endocervical canal). [5] The uterus has a rich lymphatic network. The main regional lymph nodes are paracervical lymph nodes; from there it goes to the external iliac (of which the obturator nodes are the innermost component), presacral and the hypogastric lymph nodes. The pelvic lymphatics drain into the common iliac and the para-aortic lymph nodes.

The whole uterus including the cervix is densely vascularized and their tolerance to radiation is very high. In contrast, the critical organs which are directly adjacent to the cervix like the rectum and bladder are more radiosensitive. In some cases, the very radiosensitive small or large bowel (sigmoid) may be in direct contact to the uterine wall as well.

Epidemiology:

International incidences of cervical cancer tend to reflect differences in cultural attitudes. The highest incidences tend to occur in populations that have low screening rates and a high prevalence of human papilloma virus (HPV) infection.[6] The countries that have well-advanced screening programs (e.g., the United States and the countries of western Europe) or strict religious regulation of sexual behavior (e.g., Muslim countries of the Middle East or Asia) tend to have low rates of invasive disease.

Epidemiologic studies have looked at many possible explanations for the development of cervical cancer such as young age at first intercourse, multiple sexual partners, high parity, cigarette smoking, and low socioeconomic status. Also the girls who begin engaging in intercourse before the age of 16 have a two fold increase in risk over those who begin after age 20. [7] Multiple dietary elements are currently being investigated for their potentially protective effects, including vitamins A, C, and E, as well as beta-carotene.

The intrauterine exposure to Diethylstilbestrol (DES) was found to be associated with the development of clear cell adenocarcinoma of the cervix and vagina.[8] In reports from the Registry for Research on Hormonal Transplacental Carcinogenesis, 60% of 519 cases of clear cell adenocarcinoma of the vagina or cervix were found to be related to exposure to DES or related compounds. [9,10] All these factors are linked to sexual behavior and most have been shown to be dependent risk factors. Although socioeconomic status is statistically related to patterns of sexual activity, the limited access to and use of Pap screening may also contribute to increased risk.

It appears that the most important risk factor is the acquisition of HPV infection. [11] The National Institutes of Health Consensus Statement on Cervical Cancer states that this cancer is causally related to infection with the human papilloma virus (HPV). [12] Many molecular and human epidemiologic studies have demonstrated a strong relationship between cervical intraepithelial neoplasia (CIN), and invasive carcinomas of the cervix and infection with HPV. [13,14] The HPV DNA can be identified in more than 99% of cervical

carcinomas and epidemiologic studies provide strong evidence supporting HPV infection as a necessary stage in the development of cervical cancer.[15,16]

Although cervical infection with HPV is common, the majority of these cases are self-limited and resolve within 2 years.[17,18] Two strains of HPV (16 and 18) are considered to have a high malignant potential. The HPV DNA sequences are identified in 80% to 100% of cervical carcinomas evaluated by polymerase chain reaction. [19] So the testing for HPV types (in conjunction with cervical cytology) has been approved for primary screening in women over 30 years of age. [18,20]

Who is eligible for cervical screening?

National Health Service Cervical Screening Program in United Kingdom recommended in 2003 that; All women between the ages of 25 and 64 are eligible for a free cervical screening test every three to five years.[21-23]

Pathology

Gross appearance

The gross clinical appearance of carcinoma of the cervix varies considerably and depends on the regional mode of involvement and the nature of the particular lesion's growth pattern. Three categories of gross lesions have traditionally been described. The most common is the exophytic lesion, which usually arises on the ectocervix and often grows to form a large, friable, polypoid mass that can bleed profusely. These exophytic lesions sometimes arise within the endocervical canal and distend the cervix and the endocervical canal, creating the so called barrel-shaped lesion. A second type of cervical carcinoma is created by an infiltrating tumor that tends to show little visible ulceration or exophytic mass but is initially seen as a stone-hard cervix that regresses slowly with radiation therapy. A third category of lesion is the ulcerative tumor (Figure 2) which usually erodes a portion of the cervix, often replacing the cervix and a portion of the upper vaginal vault with a large crater associated with local infection and seropurulent discharge.[22]

The concept of cervical cancer as a multi-stage disease

The cervical cancer is considered as a multistage disease from beginning of the 20th century. It is widely accepted that most invasive squamous carcinomas are preceded by an asymptomatic pre-invasive stage of the disease. At this stage, the normal squamous epithelium of the cervix is replaced by an abnormal neoplastic cells. This is the earliest stage of the disease and is known as cervical intraepithelial neoplasia (CIN).[24]

If CIN was left undiagnosed and untreated, it can progress to invasive cancer. The time span for the progression of CIN to invasive squamous cancer is variable and may be as long as 15 to 20 years. So there is strong evidence that invasive cancer can be prevented by the diagnosis and treatment of preinvasive cancer. At this microinvasive stage of cervical cancer, individual neoplastic cells or small clusters of neoplastic cells can be present deep to the basement membrane confining the CIN lesion. As the tumour progresses to the invasive stage, tongues of tumour cells extend from the epithelium of the cervix deep into the underlying stroma. The tumour may invade quite extensively locally but can invade blood vessels and lymphatic channels leading to metastatic spread.[24]

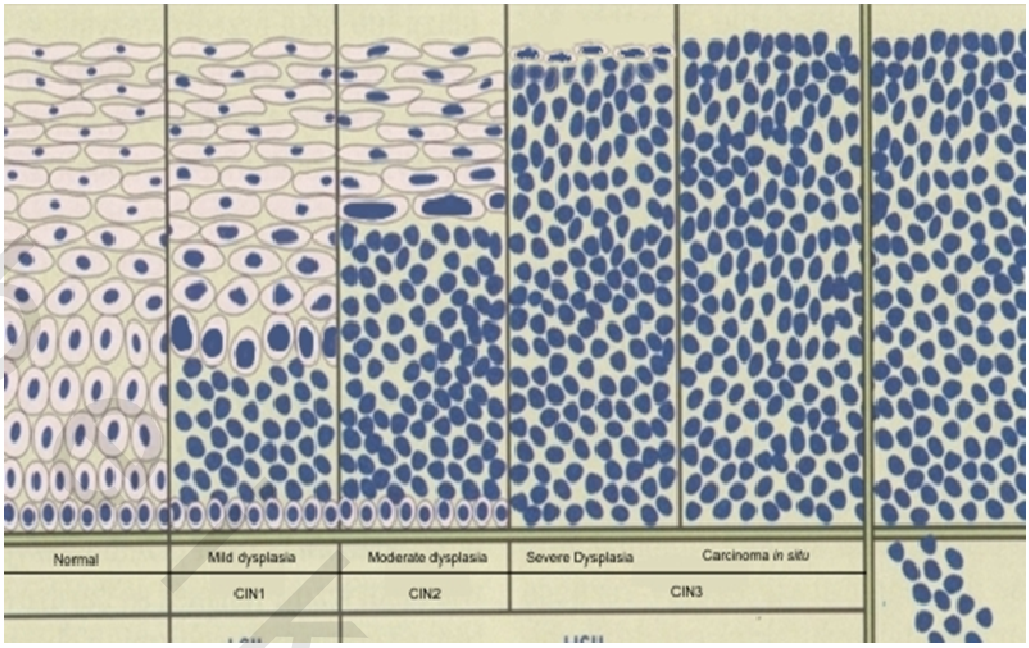

Figure (2): Graphic representation of the stages of development of squamous cervical cancer cancer and shows the progression from normal epithelium through CIN 1 ,CIN2 and CIN3 to microinvasive and invasive cancer. (24)

The World Health Organization (WHO) advised that the term carcinoma in situ (CIS) can be used to describe the lesions in which the whole thickness of the epithelium was replaced by undifferentiated neoplastic cells. WHO also recommended that the term "dysplasia" to describe the neoplastic lesions of the cervix in which only part of the thickness of the epithelium is replaced by undifferentiated tumour cells. The term Cervical Intraepithelial Neoplasia (CIN) is a single descriptive term to embrace all grades of dysplasia including carcinoma in situ under a single disease heading. Three grades of CIN are now recognized: CIN1 corresponding to mild dysplasia; CIN2 corresponding to moderate dysplasia and CIN3 corresponding to severe dysplasia and carcinoma in situ.

Prospective studies indicated that the risk of progression of CIN to invasive cancer increases with the grade of the CIN lesion .Thus the likelihood of progression is greatest in women with CIN3 and least in women with CIN1. Both the WHO terminology and the CIN terminology are in current use by histopathologists to describe preinvasive squamous carcinoma.(25)

Histological features of CIN (Figure 3)

CIN1: Indicates that undifferentiated abnormal cells are occupying the lower 1/3 of the epithelium and abnormal maturation with loss of stratification in the upper 2/3 of the epithelium.

CIN2: Means abnormal cells occupying 2/3 of the epithelium, showing loss of polarity and presence of mitotic figure.

CIN3: Indicate the abnormal cells with high n/c ratio occupying the full thickness of epithelium. They show loss of polarity, pleomorphism, hyperchromasia and mitotic figures.

Cervical Intraepithelial Neoplasia may progress to invasive cancer if not treated. The most convincing survey was carried out in New Zealand where women with carcinoma in situ were routinely followed up by cytology. Prospective follow up showed that the risk of invasive cancer after an initial diagnosis of carcinoma in situ was very high in women. Eighteen percent (18%) of the women developed invasive cancer after 10 years and 36% after 20 years.[26]

Also another survey was done by McIndoe et al,[27] that included 948 patients with carcinoma in situ (CIS) of the cervix diagnosed histologically and had been followed from five to 28 years. Among the 817 patients who had normal cytology follow-up, 1.5% developed invasive carcinoma. A second group of 131 patients continued to produce abnormal cytology consistent with cervical neoplasia. Patients with continuing abnormal cytology after initial management of CIS of the cervix are 24.8 times more likely to develop invasive carcinoma than women who have normal follow-up cytology. [27]

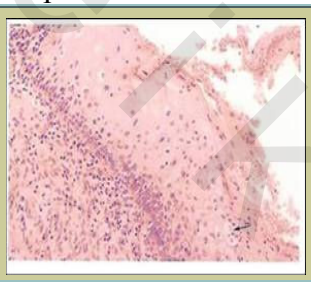	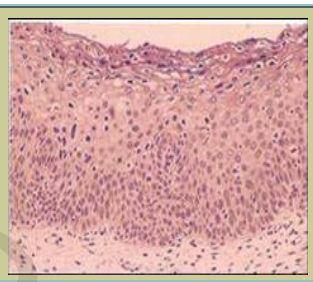	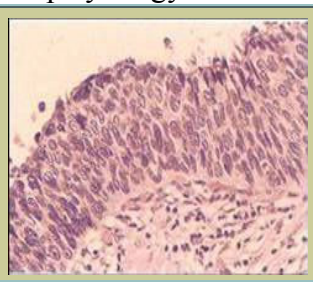
CIN1: note undifferentiated abnormal cells with high n/c ratio occupying the lower 1/3 of the epithelium and abnormal maturation with loss of stratification in the upper 2/3 of the epithelium.	CIN2: note abnormal cells with high n/c ratio occupying 2/3 of the epithelium,showing loss of polarity and presence of mitotic figure .Some abnormal maturation is seen in upper 1/3 of epithelium	CIN3: note abnormal cells with high n/c ratio occupy full thickness of epithelium. They show loss of polarity, pleomorphism, hyperchromasia and mitotic figures

Figure (3): Types and Histological features of CIN.

The Bethesda system of classification, designed to further standardize reporting of cervical cytologic findings.[28] In this system, squamous intraepithelial lesions (SILs) include all lesions that were classified as condyloma, dysplasia, or CIN in previous systems. This system divided (SILs) into two groups, low grade and high grade. The high-grade squamous intraepithelial lesions (HGSILs), which have nuclear atypia in lower and upper epithelial layers, abnormal mitoses, coarse chromatin, and loss of polarity, are usually associated with high-risk HPV types and progressing to invasive cancer (table 1).

The Bethesda system also introduced the term atypical squamous cells of undetermined significance (ASCUS). This uncertain diagnosis is now the most common abnormal Pap smear result in United States laboratories. Although most cases of ASCUS reflect a benign process, about 5% to 10% are associated with an underlying HSIL.[29]

Table (1): Bethesda System for Reporting Cervical/Vaginal Cytological Diagnosis [30]

I- Statement on specimen adequacy
II- General categorization (WNL or other)
III- Descriptive diagnosis
A- Infection **B-** Reactive or reparative changes **C-** Epithelial cell abnormalities 1- Squamous cell **a-** Atypical **b-** SIL **i-** LGSIL Cellular changes associated with HPV Mild dysplasia grade 1 (CIN 1) **ii-** HGSIL Moderate dysplasia (CIN 2) Severe dysplasia (CIN 3) Carcinoma in situ **iii** -Squamous cell carcinoma 2-Glandular cell **a**- Atypical **b-** Adenocarcinoma **c-** Other epithelial malignant neoplasms **3**- Other nonepithelial malignant neoplasms

Due to fact that the definition of microinvasive carcinoma is based on the maximum depth (no more than 5 mm) and linear extent (no more than 7 mm) of involvement, this diagnosis can be made only after examination of a specimen that includes the entire neoplastic lesion and cervical transformation zone. This requires a cervical cone biopsy.[31]

In a study of cone specimens, Reich et al. reported that 12% of microinvasive carcinomas were multifocal.[32] The lesions that have invaded less than 3 mm (International Federation of Gynecology and Obstetrics [FIGO] stage IA1) are rarely associated with metastases; while 5% to 10% of tumors that have invaded 3 to 5 mm (FIGO stage IA2) are associated with positive pelvic lymph nodes.[33]

Invasive Squamous Cell Carcinoma

Between 80% and 90% of cervical carcinomas are squamous cell carcinomas. Histologically, about 95 percent of squamous cell carcinomas are composed of relatively large cells, either keratinizing (well-differentiated) or nonkeratinizing (moderately

differentiated) patterns (figure 4,5). A small subset (< 5%) are poorly differentiated. Most authorities believe that patients with small cell squamous carcinoma have a poorer prognosis than those with large cell carcinoma. [34]

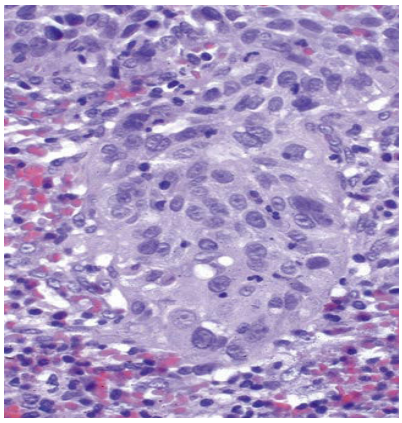

Figure (4): Microscopic picture illustrated histological features of large cell nonkeratinizing carcinoma of the cervix.

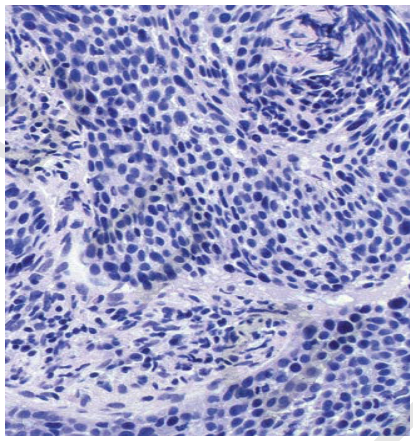

Figure (5): Microscopic picture illustrated histological features of small cell nonkeratinizing carcinoma of the cervix.

Variants of Squamous Carcinoma

A. Verrucous Carcinoma

These are very rare lesions presenting as a large sessile lesion resembling a condyloma. Histologically, it consists of a lesion with both exophytic and endophytic growth patterns, demonstrating columns of well-differentiated epithelium with intense inflammation. The recurrence rates have been as high as 50 percent.[35]

B. Papillary Neoplasms

Papillary lesions have been described in the cervix, ranging from those resembling transitional cell papillomas to those diagnosed as papillary carcinoma in situ.[36]

C. Spindle Cell (Sarcomatoid) Squamous Carcinoma

This is a rare form of squamous carcinoma demonstrating a mixture of both squamous and spindle cell features.[36]

Invasive Adenocarcinoma

Adenocarcinoma may be pure or mixed with squamous cell carcinoma (adenosquamous carcinoma). Most of cervical adenocarcinomas are of the endocervical type, that are frequently referred to as mucinous.[37] Clear cell adenocarcinomas of the cervix occur in diethylstilbestrol (DES)-exposed women. Adenosquamous carcinoma tend to have a less favorable prognosis than squamous cell carcinomas of similar stage.

The variants of adenosquamous carcinoma include adenoid basal carcinoma and adenoid cystic carcinoma. Adenoid basal carcinoma is a well-differentiated tumor that histological resembles basal cell carcinoma of the skin and tends to have a favorable prognosis. Adenoid cystic carcinomas consist of basaloid cells in a cribriform or cylindromatous pattern and tend to have an aggressive behavior with frequent metastases.[38]

Anaplastic Small Cell/Neuroendocrine Carcinoma

Anaplastic small cell carcinomas behave more aggressively than poorly differentiated small cell squamous carcinomas with poor overall survival, even for patient with stage I disease. The widespread hematogenous metastases are frequent.[39]

Clinical Presentation
Symptoms and Complaints

Many women with early disease are asymptomatic. The most common presentation of invasive cervical cancer are abnormal vaginal bleeding, post-coital bleeding, pain and vaginal discharge. A prolonged history of intermittent bleeding may be associated with a significant anemia and depletion of iron stores in the marrow. As the tumor enlarges it can cause local symptoms such as pelvic pain and difficulty with urination or defecation.

Local progression of disease may result in invasion of surrounding organs causing hematuria and dysuria secondary to bladder invasion. Also the rectal pain, bledding per rectum can be caused by rectal involvement. Hydronephrosis and uremia secondary to ureteral obstruction by tumor may occur. In seriously neglected cases, fistula formation may already be present with fecal or urinary diversion into the vagina.[40]

As the disease metastasizes to regional lymph nodes, back pain, leg swelling (especially unilateral), and neuropathic pain may occur. The incidence of nodal involvement is correlated significantly with the stage and volume of local disease, as well as depth of invasion. Stage I disease has an 11% to 18% risk of pelvic nodal involvement; stage II, 32% to 45%; and stage III, 46% to 66%.[40] Para-aortic nodal involvement has been found to be a powerful prognostic factor. The incidence of para-aortic nodal involvement is 0% to 18% for stage IB/IIA disease, 13% to 33% for stage IIB, up to 46% for stage III disease, and as high as 57% for stage IVA disease.[41]

Physical Findings

The most common finding on physical examination is an abnormal lesion on the cervix, at times necrotic and friable. Possible extension into the vaginal wall should be assessed. Determination of parametrial, sidewall, and uterosacral ligament involvement must be done through a per-rectal examination . Other areas of concern are the superficial groin and femoral lymph nodes and the supraclavicular region.

transvaginal Examination include inspection and palpation.

A- Inspection could be done using speculum that is placed at a 45 degree angle pointing slightly downward (figure 6).

B- Palpation of lesion and bimanual examination.

Palpation is done to examine the cervix regarding;

- Position, size, shape, and consistency
- mobility and tenderness

The bimanual examination is necessary to assess parametrial invasion and extension to pelvic wall (figure 7).

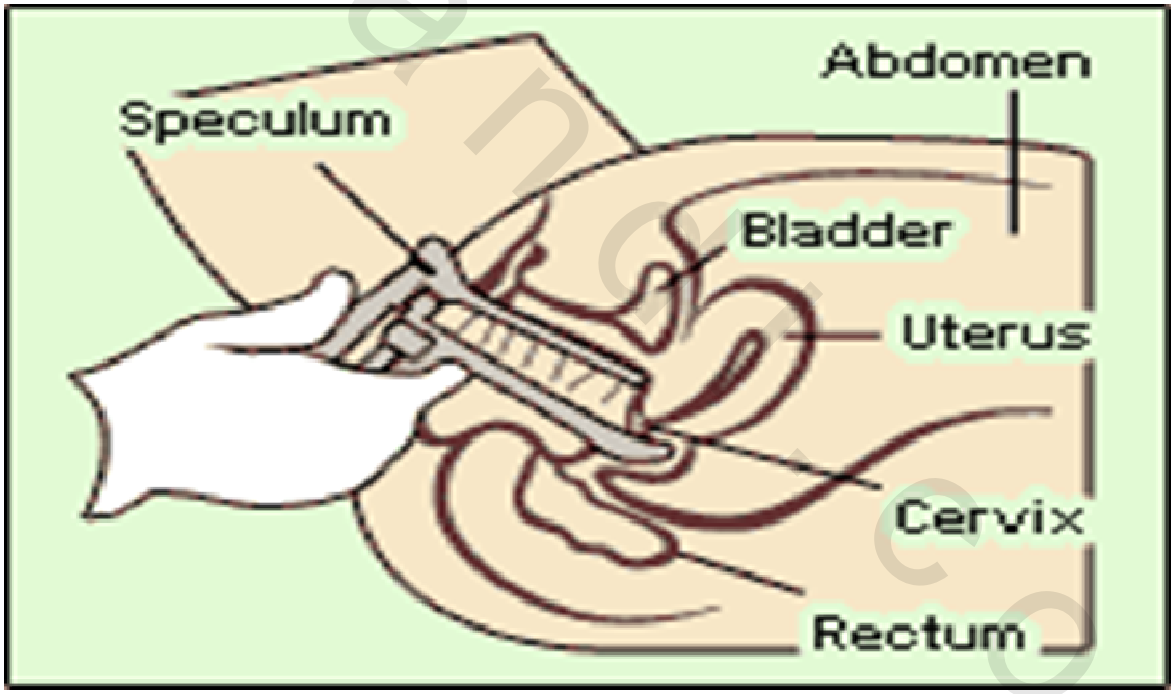

Figure (6): Diagrammatic illustration of speculum examination.

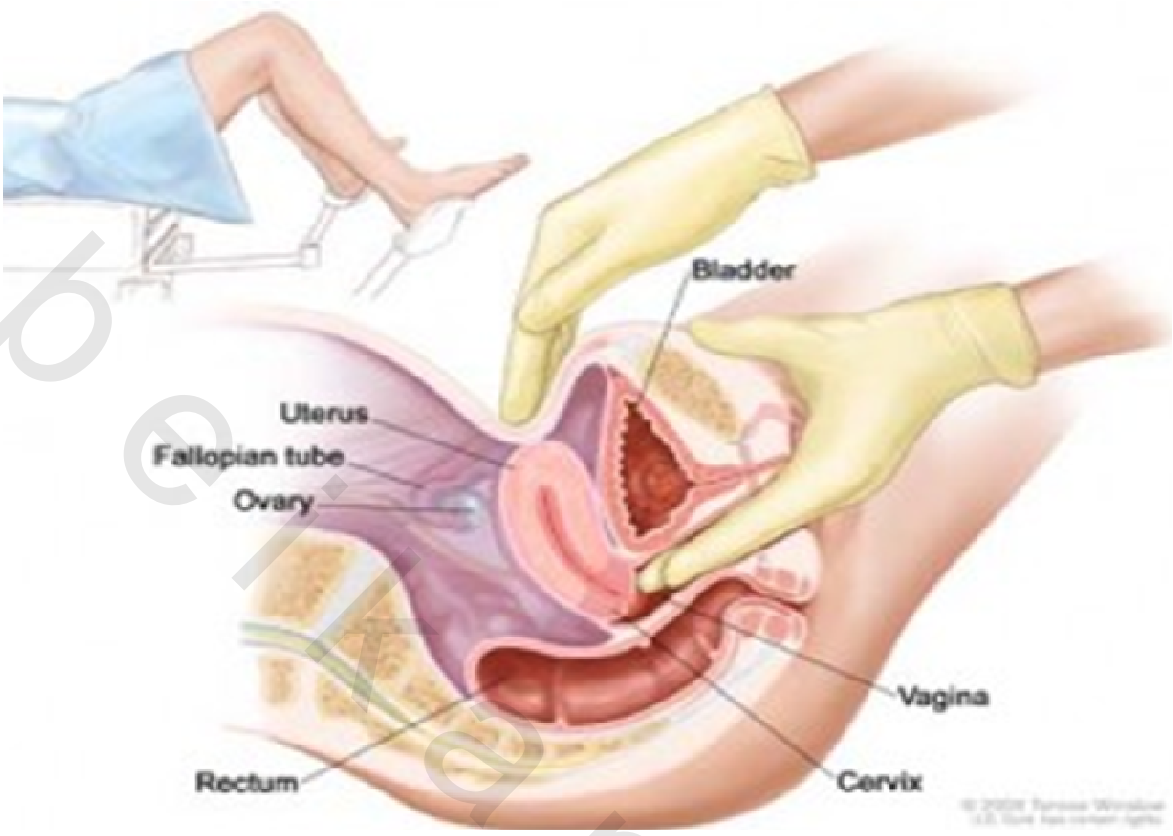

Figure (7): Diagrammatic illustration of bimanual examination.

Diagnosis

The high prevalence of the disease in unscreened populations, and the sensitivity of cytologic screening make cervical carcinoma an ideal target for cancer screening. The introduction of widespread Pap staining has led to a dramatic reduction in the incidence of invasive carcinoma on a worldwide level.

Current recommendations for screening include annual Pap smears at the age of 18 or at initiation of sexual intercourse, whichever is younger. After three consecutive yearly normal Pap smears, the frequency of Pap smears may be reduced every 2 to 3 years. Women aged 70 years and more who have had three consecutive negative test results and women who have had a total hysterectomy for benign gynecologic disease may cease cervical cancer screening.

Women with a history of CIN 2 or CIN 3 prior to or as an indication for hysterectomy should be screened until they have had three consecutive normal test results and no abnormal test results for 10 years. Women with a history of cervical cancer, women exposed in utero to diethylstilbestrol (DES), and women who are immunocompromised should continue regular screening as long as they are in reasonably good health.[42]

The rate of false-negative findings on the Pap test is about 20% to 30% in women with high-grade CIN and 10% to 15% in women with invasive cancer. However, the sensitivity of a screening program is usually increased by repeated annual testing. Detection of high endocervical lesions may be improved when specimens are obtained

with a cytobrush. Because hemorrhage, necrosis, and intense inflammation may obscure the results, the Pap smear is a poor way to diagnose gross lesions; these should always be biopsied.(43)

Colposcopy

Patients with abnormal findings on cytologic examination who do not have a gross cervical lesion must be evaluated with colposcopy and directed biopsies. Colposcopy examines the lower genital tract including the vulva, vagina, and epithelium of the cervix and opening of the endocervix. The use of acetic acid and Lugol's solution assists in highlighting abnormal and dysplastic changes.

Indications for colposcopy include an abnormal appearing cervix, persistent post-coital bleeding or discharge, persistent CIN 1, 2, or 3 on cytology, in utero exposure to DES, and ASCUS smears with positive high-risk HPV testing. In order to have an adequate colposcopic examination the entire transformation zone must be fully visualized. Endocervical curettage is recommended in all colposcopic evaluations. (44)

Cone biopsy

Cervical cone biopsy is used to diagnose occult endocervical lesions and is an essential step in the diagnosis and management of microinvasive carcinoma of the cervix. The cervical cone biopsy yields an accurate diagnosis and should be done when (1) the squamocolumnar junction is poorly visualized on colposcopy and a high-grade lesion is suspected, (2) high-grade dysplastic epithelium extends into the endocervical canal, (3) the cytologic findings suggest high-grade dysplasia or carcinoma in situ, (4) a microinvasive carcinoma is found on directed biopsy, (5) the endocervical curettage specimens show high-grade CIN, or the cytologic findings are suggestive of adenocarcinoma in situ. (45)

Large loop electrical excision procedure,

Large loop electrical excision procedure of the transformation zone involves the use of thin wire loop electrodes to remove the transformation zones in patients with low grade dysplasia. As opposed to laser ablation, and electrocautery, LEEP produces a histologically evaluable specimen. When correctly performed, some information will be available regarding proximity of the lesions to the margins.(46)

Radiological investigation

a- Transabdominal, transvaginal or preferably transrectal ultrasonography

b- Computed tomography (CT) scan of abdomen , help to check precisely the location and the dimension of the uterus and partly the gross tumour extension. It also help in detection of pelvic and abdominal LN.

c- MRI(Magnetic resonance imaging) represents the method of choice for gross tumour delineation, topography of bladder, rectum, sigmoid, and intestine. There is some advantage for MRI, as the discrimination of soft tissue structures is more accurate.

CT scan or MRI are able to detect regional and/or distant lymph node metastases; in case of suspected lymph node involvement US/CT assisted fine needle biopsies can be taken.

d- Recognizing the general difficulties in the assessment of lymphatic spread, laparoscopic approaches are being increasingly used to obtain better information about lymph node involvement and to better tailor the radiotherapy treatment strategy

e- Further diagnostic studies depend on the tumour extention: rectoscopy and cystoscopy to identify organ infiltration, intravenous pyelography to detect ureteral obstruction,

f- Chest X- ray or CT Chest to identify lung metastases; barium enema to check large bowel disease, scintigraphy to detect bone metastases.

g- Laboratory studies are performed including blood count (hemoglobin level), urine analysis, general chemistry (including creatinine).

h- Positron Emission Tomography – Computed Tomography (PET/CT) Scanning has been shown to be very effective for the staging of cervical cancer. One report has shown sensitivity and specificity of 100% .[47] The technique has been successfully employed to evaluate for early recurrence. PET/CT has been shown to be more sensitive than MR or CT in the detection of para-aortic lymph node metastases in the setting of advanced cervical carcinoma.[48] A sensitivity and specificity of 100% and 99.7% respectively have been reported for the detection of metastatic lymph nodes greater than 5 mm.[49]

The most common histological subtype of cervical cancer is squamous cell carcinoma, which represents roughly 80% of primary cervical malignancies. Most cervical squamous cell carcinomas are FDG avid. FDG uptake is commonly seen in the adjacent vagina, uterus, bladder, or parametrial region in the setting of localized tumor extension. Normal physiologic FDG excretion into the endometrium and urinary bladder may result in false positive involvement. Complete bladder voiding prior to imaging is essential in order to avoid overcalling bladder involvement.

FIGO Staging:[50]

The staging of cancer of the cervix is a clinical appraisal, preferably confirmed with the patient under anesthesia; it cannot be changed later if findings at operation or subsequent treatment reveal further advancement of the disease.

Stage 0: Carcinoma in situ, intraepithelial carcinoma

Stage I: The carcinoma is strictly confined to the cervix (extension to the corpus should be disregarded)

Stage Ia Invasive cancer identified only microscopically; all gross lesions even with superficial invasion are stage Ib cancers.

Invasion is limited to measured stromal invasion with maximum depth of 5 mm and no wider than 7 mm

Stage Ia1 Measured invasion of stroma no greater than 3 mm in depth and no wider than 7 mm

Stage Ia2 Measured invasion of stroma greater than 3 mm and no greater than 5 mm and no wider than 7 mm. The depth of invasion should not be more than 5 mm taken from the base of the epithelium, surface or glandular, from which it originates. Vascular space involvement, venous or lymphatic, should not alter the staging.
Stage Ib Clinical lesions confined to the cervix or preclinical lesions greater than stage Ia
Stage Ib1 Clinical lesions no greater than 4 cm
Stage Ib2 Clinical lesions greater than 4 cm
Stage II Involvement of the vagina but not the lower third, or infiltration of the parametria but not out to the sidewall
Stage IIa Involvement of the vagina but no evidence of parametrial involvement
Stage IIb Infiltration of the parametria but not out to the sidewall
Stage III Involvement of the lower third of the vagina or extension to the pelvic sidewall; all cases with a hydronephrosis or non-functioning kidney should be included, unless they are known to be attributable to other causes
Stage IIIa Involvement of the lower third of the vagina but not out to the pelvic sidewall if the parametria are involved
Stage IIIb Extension into the pelvic sidewall or hydronephrosis or non-functional kidney
Stage IV Extension outside the reproductive tract
Stage IVa Involvement of the mucosa of the bladder or rectum
Stage IVb Distant metastasis or disease outside the true pelvis

Prognostic Factors

The rates of survival and control of pelvic disease in cervical cancer patients are correlated with FIGO stage. The prognosis is also influenced by a number of tumor characteristics such as tumor size, depth of invasion, and grading of the invasive tumor and lymph node metastasis. Clinical tumor diameter is strongly correlated with prognosis for patients treated with radiation or surgery.[51,52]

A- Patient Age

According to some reports, age is not a prognostic factor in carcinoma of the cervix.[53] Other authors have noted decreased survival in women younger than 35 or 40 years who have a greater frequency of poorly differentiated tumors.[54]

B- General Medical Factors

Anemia and Tumor Hypoxia

Hypoxic tumors are more likely to recur locoregionally than well-oxygenated tumors regardless of whether surgery or radiation therapy is the primary local treatment. (55) In study evaluating 70 patients with stage IIB to IVA cervical cancer treated with EBRT and brachytherapy, patients with hemoglobin <11 g/dL had a 3-year survival rate of 27%, compared with 62% in those with hemoglobin >11 g/dL ($p = 0.006$).[56] The issue of whether blood transfusions to hemoglobin levels above 12 to 12.5 g/dL improve prognosis remains unsettled.

C- Tumor Factors

The rates of survival and control of pelvic disease in cervical cancer patients are correlated with FIGO stage, but prognosis is also influenced by a number of tumor characteristics.

- **Tumor Volume**

There is a close correlation between depth of stromal invasion, tumor size, and incidence of parametrial and pelvic node metastases and also survival in patients with cervical cancer.[57] A higher incidence of pelvic recurrences and distant metastases were reported by Perez et al. in patients with larger tumors treated with irradiation.[58]

Furthermore, according to Leveque et al.,[59] in patients with stage I to II adenocarcinoma of the cervix treated with RT alone or combined with radical surgery, the FIGO stage and pelvic node involvement were the most important parameters influencing overall survival.

- **Lymph node metastasis**

Lymph node metastasis is one of the most important predictors of prognosis. The survival rates for patients treated with radical hysterectomy with or without postoperative radiotherapy for stage IB disease were usually reported as 85% to 95% for patients with negative nodes and 45% to 55% for those with lymph node metastases.[60] However, this result is probably improved with concurrent chemoradiotherapy.

Inoue et al.,[61] reported that survival was correlated with the size of the largest node, and number of involved pelvic lymph nodes and survival.

- **Histology**

Most reports have shown no significant correlation of survival or tumor behavior with the degree of differentiation of squamous-cell carcinoma or adenocarcinoma of the cervix.[62]

Alfsen et al.,[62] analyzed 505 patients, 417 had tumors classified as adenocarcinoma, and 88 had tumors classified as other non-SCC. Sixty-two percent of the staged patients had clinical Stage I. In univariate analyses, histology, architectural and nuclear grade, extension to the vagina or corpus uteri, tumor length (> 20 mm) or tumor volume (> 3000 mm(3)), infiltration depth (in thirds of the cervical wall), thickness of the remaining wall (< 3 mm), vascular invasion, lymph node metastases, and patient age were significant variables in patients with FIGO Stage I disease.

- **Angiogenesis and Tumor Vascularity**

In a retrospective study of 100 patients suffering from locally advanced cervical carcinoma, the vascular endothelial growth factor (VEGF) expression in tumor biopsies was associated with a poor prognosis.[63]

- **Bax, Bcl-2, c-erbB-2, p53**

Bax protein serves as a positive regulator of apoptosis by forming heterodimers with bcl-2 protein, promoting cell survival; c-erbB-2 is a cell growth factor, and p53 a tumor suppressor gene. Ohno et al.,[64] assessed the relation between apoptosis and the expression of Bax and Bcl-2 protein during RT for cervical carcinoma in 20 patients before and after administration of 9 Gy.

The positive rate of Bax protein increased from 15% (in 3/20 patients) before irradiation to 60% (in 12/20 patients) after 9 Gy ($p = 0.0126$), suggesting that Bax protein is associated with apoptosis induced by fractionated radiation therapy.[64]

In 37 patients with stage IIIB cervical carcinoma treated with irradiation alone or combined with hyperthermia, Harima et al.,[65] reported that pelvic tumor control was associated with increased Bax expression.

- **Tumor Marker**

Elevated preoperative CA 125 levels (cutoff value, 26 U/mL) were associated with depth of stromal invasion, lymphovascular invasion, and nodal metastasis in patients with adenocarcinoma of the cervix. In patients with negative nodes, high CA 125 levels determined poor histopathological prognostic factors.[66]

In 117 patients with adenocarcinoma of the cervix, 28 of whom had preoperative carcinoembryonic antigen (CEA) levels >5 ng/mL, noted a correlation with larger tumor size, deeper cervical invasion, and lymphovascular invasion ($p < 0.001$).[67]

General principles of management

Based on all diagnostic findings including general medical status, patient age and desire to maintain fertility; the different possibilities for treatment will be decided upon by the gynaecological surgeon and the radiation oncologist.

Management of microinvasive (IA1-IA2) cervical disease :-

The prognosis of microinvasive adenocarcinoma is generally excellent, and conservative, non radical surgery is appropriate for some patients .[68,69]

Stage IA1 — Patients with stage IA1 disease can be treated with cold knife conization, simple hysterectomy is a reasonable option for women who are postmenopausal or do not wish to preserve fertility. Pelvic lymphadenectomy is not necessary.

Stage IA2 —A modified radical hysterectomy is one of treatment option for stage IA2 lesions. The added surgical morbidity of this approach compared with simple hysterectomy is minimal when performed by experienced gynecologic oncologists. In a modified radical hysterectomy, the uterine artery is ligated where it crosses over the ureter, the uterosacral and cardinal ligaments are divided midway towards their attachment to the sacrum and the pelvic side wall, respectively, so that the parametrium medial to the ureter is removed, as well as the upper one third of the vagina is resected . A pelvic lymph node dissection for stage IA2 disease is indicated.

Invasive early stage (IB1-IIA) disease

Stage IB and IIA cervical cancer can be cured by either surgery (usually radical hysterectomy, bilateral salpingo-ophorectomy and pelvic lymph node dissection) or radiotherapy (RT), which is typically administered with concurrent chemotherapy (chemoradiotherapy).

In general, the management of invasive cervical adenocarcinoma and its variants is similar, stage for stage, to that of SCC, with some minor modifications.[70] As an example, the risk of ovarian metastases is higher in women with cervical adenocarcinoma than among those with SCC (2 versus 0.5 percent in one GOG study of women with stage IB cervical cancer).[68]

Surgery is generally preferred if the patient is an appropriate candidate for surgery, given the lower rate of long-term treatment-related adverse effects.[71] However, if risk factors are identified pretreatment (eg, evidence of lymph node involvement on pretreatment imaging, tumor size >4 cm, deep stromal invasion to the middle or deep one-third, or lymphovascular space invasion as seen in the initial biopsy) that indicate the need for adjuvant therapy after surgery, then upfront chemoradiotherapy is preferred. [72]

The preference for surgery is based upon data from a prospective trial in which 343 women with stage IB and IIA cervical cancer (14 percent adenocarcinoma) were randomly assigned to primary surgery or radiotherapy (but without concurrent chemotherapy). At a median follow-up of 87 months, the five-year overall and disease-free survival rates were the same for both treatment groups (83 and 74 percent, respectively).[73]

However, multivariate analysis demonstrated a survival advantage for patients with adenocarcinoma who underwent primary surgery. It remains to be determined whether this result was due to an increased effectiveness of surgery or the absence of a benefit from radiotherapy (possibly due to the lack of concurrent chemotherapy) in women with adenocarcinoma.

As noted above, some data raise the possibility that adenocarcinomas have a poorer outcome with RT alone than do SCCs, but that relative radioresistance might be overcome through the use of concurrent chemotherapy. As a result, when RT is administered for adenocarcinoma, it is usually give concurrent cisplatin-based chemotherapy.

Extrafascial hysterectomy is not routinely performed following chemoradiotherapy. The benefit of postradiotherapy surgery was addressed in a GOG trial in which 256 women with cervical cancer >4 cm were randomly assigned to RT alone or RT followed by surgery. While the surgery group had lower rates of local relapse at five years (14 versus 27 percent), survival was not improved.(74)

A simple extrafascial hysterectomy could be considered for high risk patients (such as an initially large cervical lesion (>7 cm), lower uterine segment involvement, or a high residual tumor volume after chemoradiotherapy), although there is no consensus as to which patients fit this category.(75)

Role and extent of lymphadenectomy

Nodal metastases are the most important prognostic variable for cervical cancer. Lymph node metastases is associated with a poor outcome, particularly among those with adenocarcinoma.(70)

Pelvic lymphadenectomy is a mandatory component of initial surgery for early stage, operable cervical carcinoma (stage IA2, IB1 and IIA disease). However, unless there is gross evidence of nodal or adnexal disease at the time of visual inspection during surgery, extension of the node dissection to include the paraaortic lymph nodes is not mandatory.(76)

Indications for adjuvant therapy after hysterectomy:

The women with one or more of the following findings are considered to be at high risk for recurrent disease, and should receive adjuvant chemoradiotherapy following hysterectomy:

Positive or close resection margins
Positive lymph nodes
Microscopic parametrial involvement

Adjuvant therapy is also recommended for women at intermediate risk of recurrence (large tumor size, deep cervical stromal invasion to the middle or deep one-third, or lymphovascular space invasion), but at least for SCC, there is less consensus on the optimal form of adjuvant therapy (RT versus chemoradiotherapy). In view of the above data suggesting that adenocarcinomas have a poorer outcome with RT alone than do SCCs, but that relative radioresistance might be overcome through the use of concurrent chemotherapy.

Locally advanced (stage IIb, III, IVa) disease

Women with locally advanced cervical squamous cell cancer (greater than stage IIA disease) are best treated with primary RT (external beam plus brachytherapy) and concomitant chemotherapy.[77] Nodal involvement, particularly of para-aortic nodes, is the most important adverse prognostic factor, reducing survival by one-half.

Staging pelvic and para-aortic lymphadenectomy:

The presence of lymph node metastases is the most important prognostic factor for patients with cervical cancer.[78] While surgical evaluation should not change the stage determined by using the FIGO clinical staging system, knowledge of the extent of disease may allow for a more individualized therapeutic approach. The role of staging lymphadenectomy is controversial for women with bulky stage IB/IIA, and IIB or higher cervical cancer:

Arguments in favor of lymphadenectomy include the fact that to date, surgical staging is the most accurate method of determining lymph node involvement. Up to 26 percent of women who have no evidence of disease on radiographic studies are found to have occult para-aortic lymph node involvement.[77] Furthermore, there is a potential therapeutic survival benefit of resecting lymph nodes prior to chemoradiation, especially for women with bulky nodes.[79, 80]

Residual disease in pelvic lymph node after concomitant chemoradiotherapy for locally advanced cervical cancer has been found in up to 16 percent of patients with locally advanced cervical cancer who underwent chemoradiotherapy followed by hysterectomy and pelvic lymphadenectomy.[81]

Arguments against lymphadenectomy include the delay in the institution of primary chemoradiotherapy, and the increased risk of morbidity (especially late bowel obstructions) with the combined modality approach. The latter risk can be reduced but not eliminated by using a laparoscopic/robotic or extraperitoneal approach to lymphadenectomy, and careful RT technique.[82]

A large retrospective study has found that surgically staged patients who are found not to have involved paraaortic lymph node metastases (ie, surgically excluded paraaortic nodes) have improved survival as compared to those whose exclusion of paraaortic nodal disease was made only radiographically.[83]

So the surgery is a more sensitive method of excluding patients with microscopically involved paraaortic lymph nodes, thus selecting a more favorable subset of patients.

Many clinicians use the results of pretreatment radiographic staging studies to select women for therapeutic lymphadenectomy. Some clinicians offer pre-irradiation staging lymphadenectomy to medically fit patients if they have evidence of bulky nodes on CT scan or if a pretreatment PET scan shows uptake of FDG in the region of the infrarenal, paraaortic or pelvic lymph nodes. If both the CT and PET scan are negative, routine staging lymphadenectomy is not performed.

Other clinicians advocate pre-irradiation staging lymphadenectomy for all medically fit patients. In most cases, a laparoscopic/robotic or open retroperitoneal approach to lymphadenectomy is used.

Elective paraaortic RT is an alternative to surgical staging for locally advanced cervical cancer. The randomized trials had explored prophylactic extended field RT for women with high-risk cervical cancer and no clinical or radiographic evidence of paraaortic metastases.

The European organization for research and treatment of cancer (EORTC)[84] randomly assigned 441 women at risk for paraaortic involvement (stage I and IIB disease with proximal vaginal and/or parametrial involvement and positive pelvic LNs either on lymphangiogram or at surgery, and stage III regardless of pelvic node status on lymphangiogram) to pelvic with or without paraaortic RT.

No significant differences were found between the groups as regard to local control, distant metastases, or survival. However, the majority of patients had bulky stage II or stage III disease, with a high locoregional failure rate, possibly obscuring any potential benefit from paraaortic RT.[84]

In contrast, a survival benefit for paraaortic irradiation was suggested in a similarly designed Radiation Therapy Oncology Group (RTOG) study,[85] in which 337 women with stage IIB disease were randomly assigned to receive or not receive 45 Gy to the paraaortic region in addition to standard pelvic RT. Although locoregional control rates were similar, the 10-year survival rate was significantly better for those undergoing extended field RT (55 versus 44 percent). Treatment-related toxicity was greater, particularly among those who underwent prior surgery for any reason.

The relative benefit of extended field RT alone compared to concomitant chemoradiotherapy plus pelvic only RT was tested in RTOG 90-01. This study randomly assigned 403 women with advanced cervical cancer confined to the pelvis (stages IIB through IVA or stage IB or IIA with a tumor diameter of at least 5 cm or involvement of pelvic nodes) to RT alone (45 Gy) followed by low dose rate intracavitary irradiation, or RT with concomitant cisplatin (75 mg/m2 on days 1 and 22) plus infusional 5-FU (1000 mg/m2 per day days one through four and 22 through 25 of RT) followed by low-dose-rate (LDR) intracavitary brachytherapy concomitant with the third cycle of chemotherapy.[86]

With a median follow-up of 6.6 years for the 228 surviving patients, women with stage IB-IIB disease treated with chemoradiotherapy had significantly superior overall and DFS rates compared to those receiving extended field RT alone. For those with stage III to IVA disease, pelvic RT plus chemotherapy was associated with significantly better DFS; however, only a trend was noted toward better overall survival ($p = 0.07$). It is unclear whether the addition of extended field RT to concomitant chemotherapy may improve upon these results.[87]

Concomitant chemoradiotherapy versus RT alone :

The benefit of cisplatin-based concomitant chemoradiotherapy compared to RT alone for locally advanced cervical cancer has been confirmed in multiple trials, all of which

study different populations, and slightly different chemotherapy regimens. The following represents the range of findings:

A GOG trial randomly assigned 368 women with locally advanced disease (stage IIB, III, or IVA) to RT concurrent with hydroxyurea (HU, 80 mg/kg twice weekly during RT) versus the same RT dose plus concomitant cisplatin (50 mg/m2 on day 1 and 29) and 5-FU (1000 mg/m2 by continuous infusion on days 2 to 5, and 31 to 33). Cisplatin-based chemoradiotherapy was associated with a significant improvement in both PFS and overall survival.[88]

A second GOG study randomly assigned 526 women with stage IIB, III, or IVA cervical cancer to RT with one of three different chemotherapy regimens: HU alone (3 g/m2 twice weekly for six weeks), cisplatin alone (40 mg/m2 weekly during RT), or cisplatin (50 mg/m2 on days 1 and 29) plus infusional 5-FU (1000 mg/m2 per day on days 1 to 4) and HU (2 g/m2 twice weekly for three weeks). In the latest report (106 month median follow-up), five-year survival rates were significantly better with both cisplatin alone and cisplatin/5-FU/HU (60 and 61 percent, respectively) than with HU alone (40 percent).[89]

Meta-analysis including13 trials andomly assigned patients with FIGO stage IA to IVA disease to chemoradiotherapy versus RT following hysterectomy. Compared to RT alone, combined chemoradiotherapy was associated with a significant 19 percent reduction in the risk of death (which translated into an absolute improvement in five-year survival from 60 to 66 percent), a 22 percent improvement in DFS, and a significant decrease in both local and distant recurrence rates. Benefit was seen across all disease stages, although the survival benefit was most pronounced in patients with earlier stage (ie, stage IA-IIA) disease.[90]

In an international multicenter randomized trial, 515 women with IIB to IVA cervical cancer were randomly assigned to concurrent cisplatin (40 mg/m2 weekly for six weeks) with external beam RT (50.4 Gy) followed by brachytherapy versus the same dose of weekly cisplatin plus gemcitabine (125 mg/m2 weekly for six weeks) concurrent with pelvic RT (50.4 Gy), and followed by brachytherapy. The experimental group also received two additional 21-day cycles of adjuvant gemcitabine (1000 mg/m2 on days 1 and 8) and cisplatin (50 mg/m2 on day 1 only) after brachytherapy. At three years, gemcitabine-containing therapy was associated with significantly better PFS (hazard ratio [HR] for progression 0.68, 95% CI 0.49 to 0.95; three-year PFS 74 versus 65 percent) and overall survival (HR for death 0.68, 95% CI 0.49 to 0.95). However, these improvements came at the cost of greater treatment-related toxicity. Grade 3 and 4 toxicities during therapy were more frequent overall in the experimental arm (87 versus 46 percent), and there were two deaths.[91]

Patients with paraaortic metastases

The benefit of adding chemotherapy to radiation therapy (RT) in patients with paraaortic nodal metastases (an indication of distant rather than regional spread) is unclear. An RTOG trial included 30 patients with clinical stage I to IV disease (17 stage I or II) and positive paraaortic nodes who received twice daily (hyperfractionated) extended field RT plus intracavitary brachytherapy and two to three cycles of concomitant chemotherapy (cisplatin 75 mg/m2 on days 1 and 22, and infusional 5-FU 1000 mg/m2 daily, days 1 to 4,

and 22 to 25). Paraaortic RT was delivered at 1.2 Gy per fraction twice daily in an attempt to safely escalate the dose (median dose 48 Gy). The two and four-year overall survival rates were 46 and 29 percent, and locoregional failure rates at one and two years were 40 and 50 percent, respectively.[92]

While acute toxicity remains high with the combination of chemotherapy and extended field RT, the survival advantages demonstrated in the majority of randomized chemoradiotherapy trials (although the group with involved paraaortic nodes was excluded) argues in favor of this approach in this high risk group. Some groups have attempted to decrease toxicity by utilizing intensity modulated radiation therapy (IMRT). IMRT may limit the bowel and bone marrow toxicity associated with Extended field radiotherapy (EFRT).[93]

Furthermore, IMRT may allow for selectively boosting the dose to sites of node positivity, as is done for pelvic lymph nodes, without an increased probability of bowel toxicity.[94]

Neoadjuvant chemotherapy

SCC of the cervix is a chemosensitive neoplasm particularly when cisplatin-based regimens are used, and neoadjuvant chemotherapy may be an accepted approach for patients with locally advanced disease. Adenocarcinomas are similarly chemotherapy sensitive, at least in the setting of advanced disease. The use of neoadjuvant chemotherapy may be beneficial in selected women.

This strategy was investigated in a report in which 16 women with cervical adenocarcinoma or adenosquamous carcinoma received cisplatin, etoposide, and mitomycin (median three courses) prior to radical hysterectomy. There were three complete and five partial responders (objective response rate 50 percent). Of the 12 patients who subsequently underwent surgery, histologic changes correlated well with the clinical response.[95] The long-term results are not available, and whether this strategy provides superior outcomes over chemoradiotherapy is unknown.

Stage IVB, persistent and recurrent disease

Following radical hysterectomy or definitive chemoradiotherapy for early stage cervical squamous cell cancer, the predominant site of disease recurrence is local (vaginal apex) or regional (pelvic sidewall). Exenterative surgery is an option only for those few patients with centrally relapsed disease.

Patients with more extensive primary or locoregionally relapsed disease or distant metastatic disease are usually treated with palliative chemotherapy. There are studies that have attempted to evaluate the response of adenocarcinoma to chemotherapy. Cisplatin is the most active single agent.[96]

The benefits of combination versus single agent chemotherapy have not been proven for cervical adenocarcinoma. For patients with SCC, the benefits of combination cisplatin-based chemotherapy as compared to single agent therapy include significantly higher response rates, and longer progression-free survival; however, the side effect profile is worse and the survival benefit, if it exists, is modest.[97]

Based upon favorable results from a phase II GOG study investigating the role of single agent bevacizumab in women with predominantly SCC, 452 women with stage IVB or persistent and recurrent CC after standard treatment were enrolled in GOG 240, a randomized Phase III trial. This study was designed to answer two important questions, ie, whether topotecan in combination with paclitaxel was superior to the association of cisplatin and paclitaxel and whether the addition of bevacizumab 15 mg/kg to either regimen improved OS. More than 70% of patients in each group had previously received platinum-based therapy as a radiosensitizing strategy. Patients were randomly assigned to one of four treatment groups; two of the treatment groups received bevacizumab. At a median follow-up of 20.8 months, bevacizumab-treated patients lived for a median of 3.7 months longer than those who did not receive bevacizumab. The PFS and response rate were also better in patients who received bevacizumab than in those who received chemotherapy alone.[98]

Surgical resection may be useful in carefully selected patients with cervical adenocarcinomas who have isolated pulmonary metastases.

External beam planning for locally advanced cervical cancer

The treatment of cervical cancer has been and still is the domain of radiotherapy.[99] Currently, the two main modalities of irradiation are external photon beam and brachytherapy. External irradiation is used to treat the whole pelvis and the parametria including the common iliac and para-aortic lymph nodes, whereas central disease (cervix, vagina, and medial parametria) is primarily irradiated with intracavitary brachytherapy.

In the last decade effort has been put into combining radiotherapy with other treatment modalities, mainly chemotherapy,[74, 86] or hyperthermia[100] resulting in better locoregional control rates and improve survival rates. However, treatment results are still not satisfactory, and radiation oncologists continue their search for strategies to optimize the radiotherapy itself.

This is a challenge, because cervical tumors are large, can regress more or less rapidly and move during therapy, and are closely surrounded by critical organs. External treatment using the four-field box technique with field borders generated according to the bony anatomy fail to encompass the target volume adequately in a number of patients.[101] Therefore, visualization of the primary tumor process and its surrounding organs is one of the crucial steps in the process of improving radiotherapy.

Imaging techniques such as computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) visualize the primary cervical tumor, the pathologic lymphatic nodes, and the surrounding organ.[102, 103] Magnetic resonance imaging is superior to CT or examination under anesthesia in detecting the boundaries of the cervical tumor mass, with respect to parametrial invasion, infiltration into the uterus, and its invasion into the bladder and rectum.[104] Besides this advantage in the pretreatment setting, the regression of tumor volumes due to irradiation can be analyzed with repeated MR imaging .[105, 106]

According to the findings of Hatano et al.,[106] substantial tumor regression can be expected after having delivered a dose of 30 Gy. In addition to this progress in the process of defining the radiation target more precisely, radiation techniques themselves have

developed rapidly in recent years. Newly developed treatment strategies and planning techniques make it possible to optimize the doses to the target volumes without increasing the dose to the critical organs.

Three dimensional conformal radiation therapy (3D-CRT) as well as intensity-modulated radiation therapy (IMRT) clearly improve dose conformity compared with conventional planning.[107, 108]The conformal dose distributions and the steep dose gradients generated around target volumes created by 3D-CRT and IMRT planning require an accurate treatment setup and repeated monitoring to prevent a geographic miss during radiotherapy.

The advent of conformal radiotherapy techniques and technology has allowed for more normal tissue sparing and sparked interest in the use of intensity-modulated radiotherapy (IMRT) for the treatment of cervix cancer. While planning studies have predicted substantial organ at risk (OAR) sparing, the clinical outcomes have been more modest. The rates of grade 2 gastrointestinal (GI) toxicity experienced by patients undergoing IMRT for either definitive cervix cancer or post-operative cervix/endometrial cancer have ranged from 10 to 85%.[107, 109]

Roeske et al.,[110] noted that many of their whole-pelvis IMRT patients developed acute toxicity at a rate comparable to those treated with conventional pelvic fields. The reasons for this wide range are multifactorial, in part due to differences in target volumes and the smaller amount of bowel within the pelvis for definitive cervix cancer versus postoperative cases, as well as different planning margins used by the different groups.

Gerszten et al.,[109] noted that the inability to clearly define areas at risk by computed tomography (CT) criteria resulted in generous planning target volumes (PTVs), which closely approximated traditional large pelvic fields. Additionally, the current incomplete understanding of the complex tumor and normal organ motion and deformation dynamics influences PTV margins and conformal treatment strategies, which impacts the volume of normal tissues irradiated.[111]

So in the present study of patients with cervical cancer, we compared conformal, and IMRT plans with respect to target volume coverage and critical organ sparing. Internal organ motion and tumor regression were taken into account by generating the treatment margins, i.e., the clinical target volume (CTV) and planning target volume (PTV) expansions. Also we investigated, whether IMRT plans would improve the target coverage and critical organ sparing.

Treatment Volume of External Beam Radiotherapy

In treatment of invasive carcinoma of the uterine cervix, it is important to deliver adequate doses of irradiation not only to the primary tumor but to the pelvic lymph nodes to maximize tumor control.[86]

Borders for conventional radiotherapy technique (Figure8)

Superior = L4/5;

Inferior = 3 cm below most inferior vaginal involvement as marked by gold seeds (often at inferior obturator foramen);

Lateral = 2 cm lateral to pelvic brim;

Posterior = include entire sacrum;

Anterior = 1 cm anterior to pubic symphysis.

Treat inguinal nodes if stage IIIA (lower 1/3 vagina). Inferior border is vaginal introitus or flash.

If common iliac nodes involved, raise superior border to allow for at least a 4 cm margin (~L3/4 level).

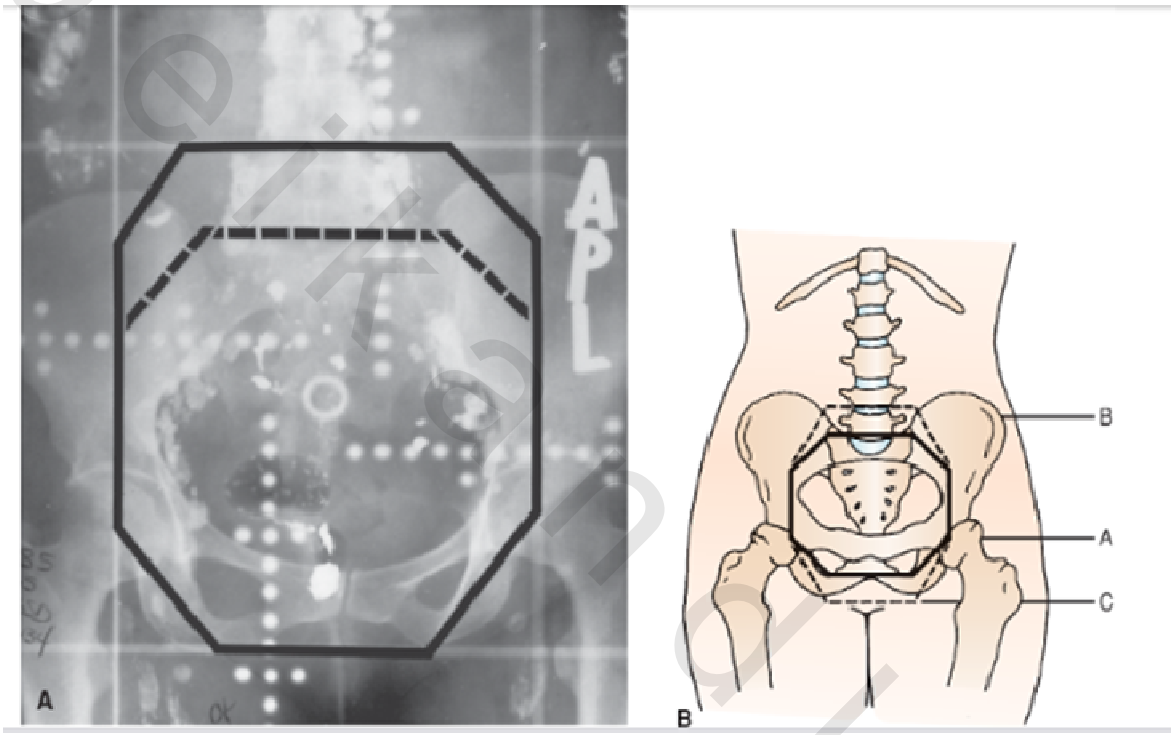

Figure (8): A Anteroposterior simulation film of the pelvis illustrating portals used for external irradiation. The 15 by 15 cm portals at source-to-skin distance are used for stage IB (broken line), and 18 by 15 cm portals are used for more advanced disease (solid line). This allows better coverage of the common iliac lymph nodes. The distal margin is usually placed at the bottom of the obturator foramina. B: Diagram of pelvic portals used in external irradiation of carcinoma of uterine cervix. Standard portal for stage IB tumors is outlined (solid line indicated as A). When the common iliac nodes are to be covered, the upper margin is extended to the L4-5 space. If there is vaginal tumor extension, the lower margin of the field is drawn at the introitus.

Borders for conventional EFRT for paraaortic nodes (Figure 9)

Superior border = T12/L1,

Lateral= encompass tips of transverse processes.

The midline block may be used to avoid excess dose adjacent to the implant and to deliver higher dose to potential tumor bearing regions outside the implant. Midline block reduces dose to bladder and rectum, but may underdose sacrum. Superior border of midline block is at a midsacroiliac joint. Midline blocks narrower than 5 cm may include the ureters which are ~2–2.5 cm from midline and is placed at end of 40 Gy before BT.

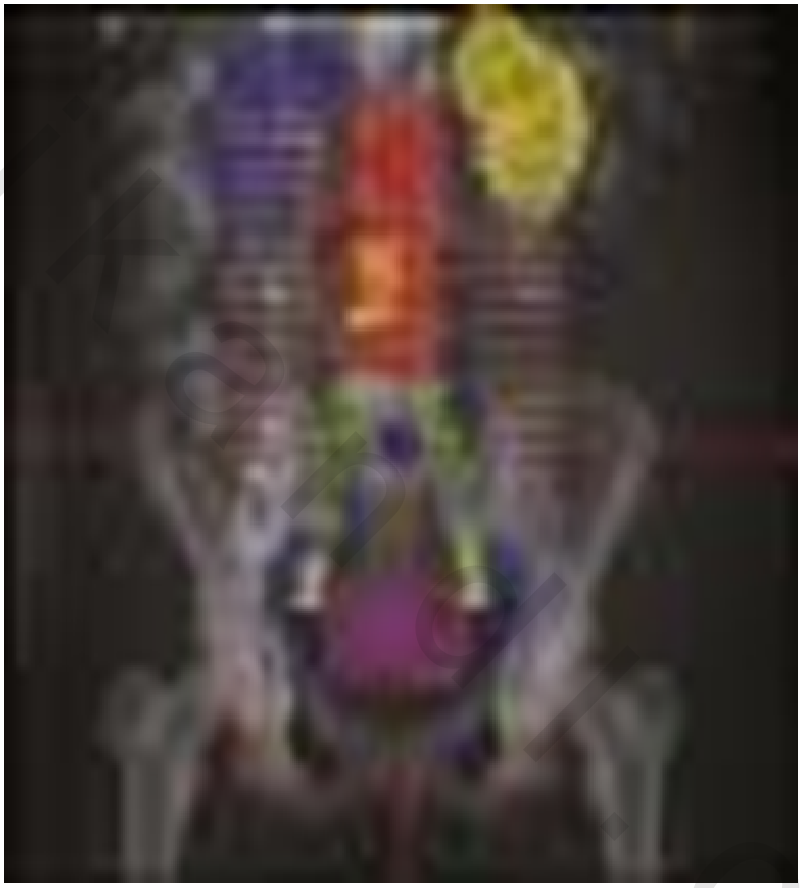

Figure (9): Reconstructed DRR film of extended field for external irradiation of pelvic and para-aortic lymph nodes.

Delineation of Target Volumes for conformal and IMRT radiotherapy technique:
Gross Tumor Volume (GTV)

Tissues that are known or suspected to contain gross disease should be carefully contoured. The CT images usually provides inadequate detail for accurate delineation of the GTV in central structures (cervix, vagina, and paracentral tissues). MRI is an important source of supplementary information in most cases. The extent of vaginal involvement should be carefully defined using marker seeds placed during clinical examination before simulation.

Clinical Target Volume (CTV)

The CTV encompasses the GTV as well as any tissues within the treatment volume that are at risk for containing microscopic disease. This should include lymph nodes that drain the involved site and adjacent perinodal soft tissue. The CTV should also include paracervical and paravaginal soft tissues that are at risk for tumor involvement.

For most cases of intact cervical cancer, the internal (hypogastric and obturator), external, and common iliac lymph nodes are included in the CTV. The presacral lymph nodes are usually included, and in selected cases, inguinal or paraaortic lymph nodes may require treatment. Because the lymph nodes lie along the paths of the iliac vessels, identification of the CTV usually begins with identification of these vessels. The regional CTV should include the vessels with surrounding perivascular soft tissue and lymph nodes.

Mundt et al.,[112] recommend that the contour encompass the common iliac, external iliac, and hypogastric vessels with a 2-cm margin. Approximately 1–2 cm of tissue anterior to the S1, S2, and S3 sacral segments is usually added to the CTV to include the presacral lymph nodes and uterosacral ligaments in patients who have cervical cancer. The CTV also must include the uterus and cervix (if present) and at least the upper half of the vagina with adjacent paravaginal and parametrial tissues.

Planning Target Volume (PTV):

Margins for Set-up Variation in patient must be carefully considered in designing highly conformal IMRT treatment plans. Some expansion of the CTV is usually required to account for these variations; this expanded volume is referred to as the planning target volume (PTV). The amount of expansion and the priorities for coverage of the PTV should take into careful account the reproducibility of the patient's set-up, the critical structures within the expanded volume, and the impact of target volume expansion on the normal tissue sparing relative to more conventional treatment techniques. In most cases, a PTV margin of 5–10mm is needed unless the patient is being repositioned with daily pretreatment imaging (figure 10).[111]

Organs at Risk (OAR)

Most of the major complications of high-dose pelvic radiation therapy involve bladder, rectum, or small bowel, and conformal and IMRT plans are usually designed to minimize the radiation dose to these structures. These structures should always be delineated on CT scans used for treatment planning. For treatment planning, the entire rectum is usually contoured up to the level of the splenic flexure. The patients should be instructed to have a full bladder during simulation and treatment. The bladder wall is contoured for use as an avoidance structure during treatment planning.

The bowel-containing intraperitoneal space is usually contoured as a single structure. All bowel should be contoured within and 1–2 cm above and below the target volume structures; additional bowel may need to be contoured if noncoplanar beam arrangements are being considered, although this is rarely required in gynecologic treatments. No attempt should be made to outline individual loops of small bowel separately; doing so is labor-intensive and unrealistic because bowel moves freely within the peritoneal cavity. Other normal tissue structures should be defined if they are within the plane of radiation

treatment. The kidneys, spinal cord, and liver should be contoured if the target volume extends to abdominal structures.

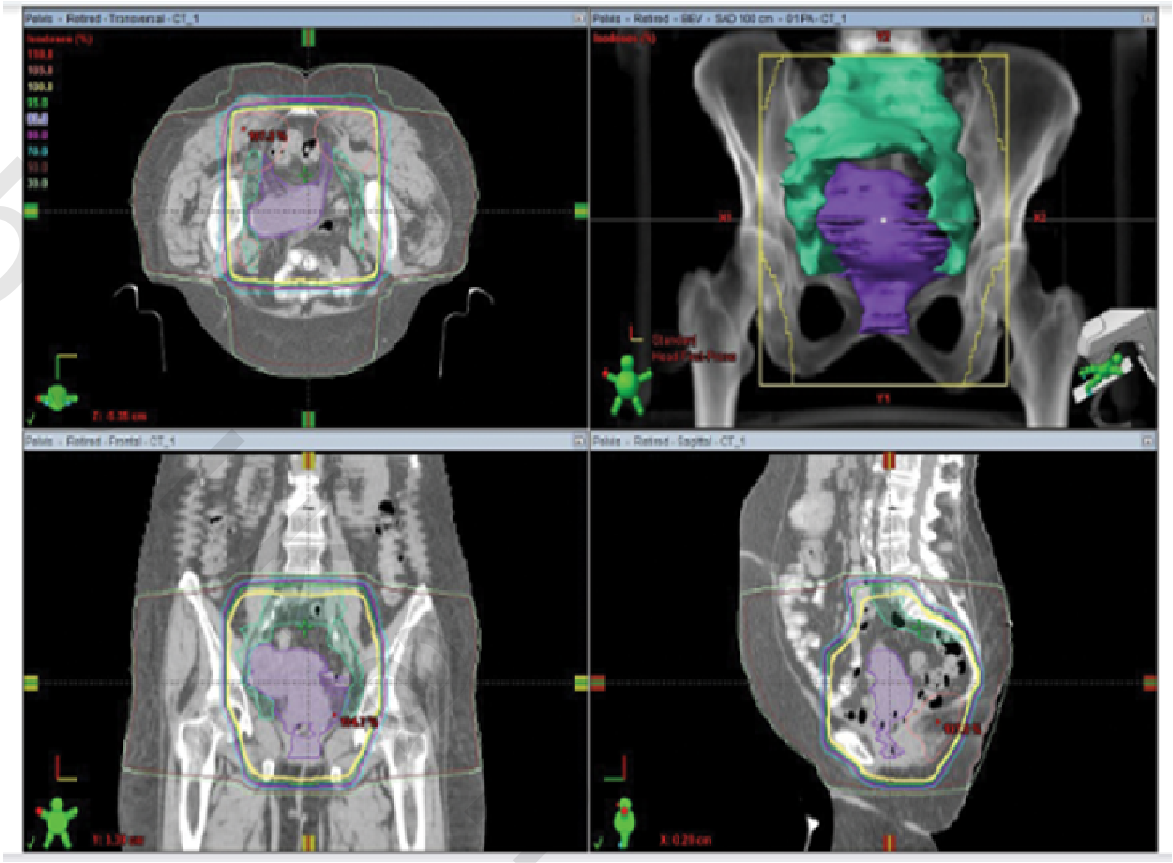

Figure (10):- Example of conformal whole pelvis radiotherapy treatment for patient with cancer cervix.

Brachytherapy (BT) component of cervical cancer management

Intracavitry brachytherapy (ICBT) is an essential component of cervical cancer management and has a high therapeutic index by delivering a high dose to the primary cervical lesion and lower doses to adjacent organs, resulting in increased local control and survival without increased in toxicity.(113)

However, the routine intracavitary brachytherapy may not be feasible or adequate to treat patients with locally advanced disease or with distorted anatomy, so these patients may be treated adequately with interstitial brachytherapy to achieve excellent locoregional control and a reasonable chance of cure with acceptable morbidity.(114)

However the doses delivered to tumor and normal tissues from ICBT are difficult to quantify accurately in conventional brachytherapy planning. To ensure consistency in the reporting of ICBT applications in cervical cancer, the International Commission on Radiation Units and Measurement (ICRU) recommended a number of parameters for doses and volumes to be considered. These include points A and B, representing the doses in the parametria and the pelvic wall, and rectal and bladder ICRU points representing the organs at risk (OARs), respectively (figure 11).(115)

- *Point A*
  - 2 cm sup and 2 cm lateral to the os in the plane of the Apparatus
  - Represents the medial parametrium, where the ureter and the uterine artery intersect
- *Point B*
  - 2 cm sup to os and 5 cm lateral midline of pelvis
  - Represents the parametrial tissue
  - Approximately 25% of point A dose
- *ICRU Rectal point*
  - The level of the midpoint of the ovoid
  - Represents the anterior rectal wall
- *ICRU Bladder Point*
  - Center of the Foley balloon
  - Represents the posterior edge of the equator of the Foley balloon
- *Point P*
  - Intersection of horizontal and vertical lines tangential to the acetabulum
  - Represents the pelvic side wall
  - Denotes minimum dose to external Iliac LNs
  - Approximately 10% of point A dose

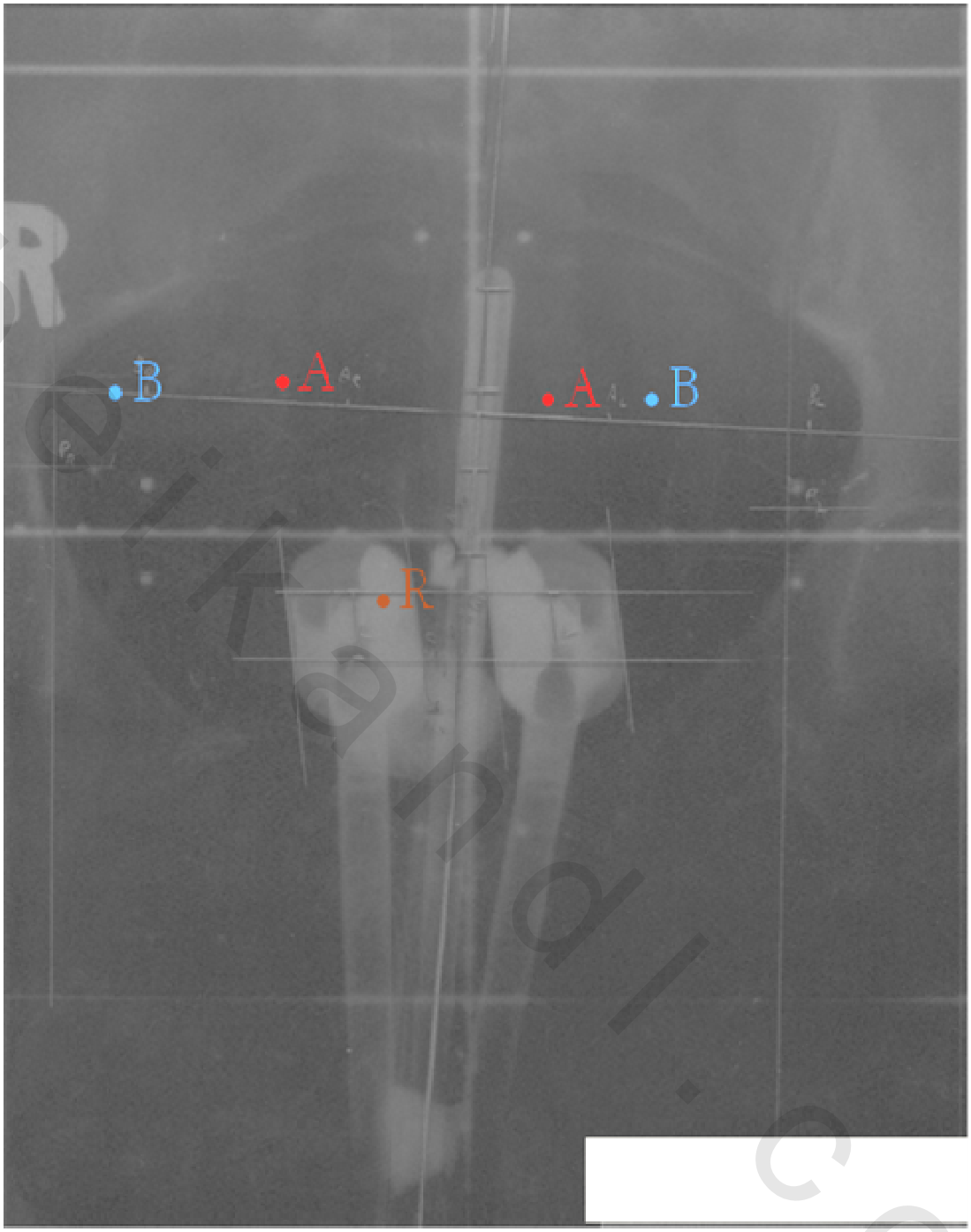

Figure (11): Orthogonal film with applicator in place illustrating different ICRU points.

Physicians have used these reference point doses to report treatment intensity and to estimate the maximal dose to normal tissues, which can predict late complications. However, the conventional plan in treating cervical cancer may not correspond with the individual extent of the tumor. This may result in either undercoverage of the tumor or overdosage of the surrounding normal tissue. Also The rectal and bladder reference dose points of the International Commission on Radiation Units (ICRU) 38 are the standard for reporting normal tissue doses with BT. However, these points are based on plain films and

two-dimensional (2D) BT planning and do not relate to the maximum dose delivered or toxicity.[116]

Three-dimensional (3D) imaging allows for the delineation of the organs at risk (OAR), including the bladder, rectum, and sigmoid. In 2005, the GEC-ESTRO [117] published guidelines for magnetic resonance (MR)-based contouring of tumor volumes in cervical-cancer BT. *Gross tumour volume* (BT) for BT includes macroscopic tumour extension at time of BT as detected by clinical examination and as visualised on MRI: High signal intensity mass(es) (FSE, T2) in cervix/- corpus, parametria, vagina, bladder and rectum. In patients treated with upfront BT or with BT alone, GTVB is identical with GTVD.

High risk CTV for BT (HR CTVB1, HR CTVB2,.) carrying a high tumour load, includes GTVB, whole cervix and the presumed extracervical tumour extension at time of BT. In limited disease GTVB is identical with GTVD . In advanced disease, the presumed tumour extension is defined by means of clinical examination (visualisation and palpation) and by MRI findings at time of BT GTVB. Pathologic residual tissue(s) as defined by palpable indurations and/or residual grey zones in parametria, uterine corpus, vagina or rectum and bladder on MRI are included in HR CTVB. No safety margins are added.

Intermediate risk CTV for BT carrying a significant microscopic tumour load, encompasses high risk CTV with a safety margin of 5– 15 mm. Amount of safety margin is chosen according to tumour size and location, potential tumour spread, tumour regression and treatment strategy.

GEC-ESTRO (II)[118] recommended the reporting of the minimum dose to the most irradiated tissue volume (D0.1, D1, and D2cc). This was based on the assumption that the OAR received the full dose of external-beam radiation and that the brachytherapy dose to the OAR should be recorded per fraction in order to calculate the worst-case scenario of cumulative dose received.

The modern approach in treatment planning for cervical carcinoma is based on MRI sections or CT and on a 3D dose distribution. This allows better assessment of dose distributions in different volumes, such as the gross tumor volume (GTV), clinical target volume (CTV), and OARs (rectum, bladder, and intestines).