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Review Article

Management of Cancer Cervix

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Abstract

Cancer cervix is the most common gynaecologic malignancy. About 86% of cervical cancer cases and 13% of female cancer occur in developing countries. As the causative agent is Human Papilloma Virus (HPV), this cancer is preventable by regular screening and HPV vaccination. HPVDNA vaccines are promising approach for antigen-specific T cell mediated immunotherapy against HPV infection and they have significant therapeutic potential for clinical application in the treatment of HPV related cervical cancer, reducing morbidity, mortality, and improving quality of life. Trials show that vaccination against HPV-16 and 18 reduces newer and persistent infections with 92% and 100% efficacy respectively. Eighty five percent of cervical cancers are of squamous cell type and others of adenocarcinoma type and very few other rare tumors. FIGO stages I-IIA are referred as early stage disease and stages IIB and higher are advanced disease. For early stage invasive cancer surgery is the choice and for advanced stage radiotherapy (RT) with or without chemotherapy is the choice. Treatment of cancer cervix requires multidisciplinary approach. Prognosis depends on-FIGO stage, tumor size, and surgical staging. Lymph node involvement in early stage cervical cancer, Stage I to IIA-single lymph node *vs.* multiple lymph nodes metastasis, stage IIB to IV, no lymph node involvement *vs.* one positive lymph node *vs.* multiple involved nodes, Microscopic *vs.* macroscopic nodal involvement will affect the prognosis. Clinical stage at diagnosis is the single most important prognostic factor for cervical cancer during pregnancy.This review article focused on recent trends of management protocols and newer trials on cervical cancer.

Keywords: Cervical cancer; HPV virus infection and related cancer; Management of cancer

Introduction

Cervical cancer is the third most common cancer in woman following breast and colorectal cancer in all age group and second most common in woman of reproductive age group [1,2]. As per WHO estimation in 2008 worldwide there were 529,409 new cases of cancer cervix and 274,288 deaths. The ratio of mortality to incidence is 52% [2]. The low incidence of cervical cancer in developed countries proves the success in regular screening. The majority (85%) of cases are squamous cell carcinoma and rest are adenocarcinoma [2,3].

Risk factors and etiopathogenesis

Other than demographic risk, HPV a sexually transmitted infection, early coitarche, multiple sexual partners, multi-parity, smoking, and lack of regular Pap smear screening are the associated risk factors for cervical cancer [3].

Human papilloma virus (HPV), infection

(HPV 16 and 18) is the etiologic agent of cervical cancer is now proved by clinical, epidemiological and molecular data [3,4]. The HPV viral oncogenes integrate into the cellular genome during cell divisions and differentiation of basal epithelium to stratified epithelium and high risk HPV DNA enhances replication of E6 and E7 genes. When viral DNA is in episomal conformation (inside nucleus but not bound to host DNA), form low-grade squamous intraepithelial lesions. When HPV DNA is in integrate conformation (binds to host cellular DNA), high-grade squamous intraepithelial lesions and invasive carcinomas develop [5]. They affect cell cycle control, independent cell growth regulation, resistance to apoptosis, immune response escape, and angiogenesis, and progression to malignancy [6].

Lower socioeconomic and educational status, older age are independently related to lesser rate of cervical cancer screening due to limited access or responsibility. Active and passive cigarette smoking increases the risk of HSIL and invasive cervical cancer by two to three folds. Current smoking alters the immunity system leads to reduced clearance of High risk HPV and increases chances of developing squamous cell carcinoma more than adenocarcinoma [7]. Woman with prior seven full term pregnancies have fourfold increase risk and those with one or two have twofold increase risk as compared with nulliparous for developing cervical cancer [3].

Long term combined oral contraceptive (COC) Pill use increase the risk up to four fold of developing cervical cancer as studies shows positive correlation between a low serum estradiol: progesterone ratio and shorter overall cervical cancer survival in premenopausal women [8] Estrogen acts as an anti-apoptotic agent permitting proliferation of cells infected with oncogenic HPV. Current and within 9 years of COC users have significantly higher risk of developing both squamous cells and adenocarcinoma of cervix. Multiple sexual partners (>6 lifetime partner), and coitarche before 20 years of age increases the risk of developing cervical cancer. Abstinence from sexual activity and use of barrier contraception during sexual intercourse decreases the cervical cancer risk [9].

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Genetic susceptibility

Genetic susceptibility is found to be the cause for less than 1% of cervical cancers. Women with history of a first degree biologic relative affected with a cervical tumor have a twofold relative risk of developing a cervical tumor [10]. Tumor necrosis factor (TNF) initiate the cell apoptosis, Polymorphism with Tp53 involved in apoptosis and gene repair and some HLA gene anomalies are found to be associated with an increased risk of HPV infection progressing to cervical cancer [11-13]. The chemokine receptor-2(CCR2) gene on chromosome 3p21 may disrupt the immune response to HPV and also influence the genetic susceptibility of an individual to cervical cancer [14]. The CASP8 gene has a polymorphism in the promoter region and is associated with a reduced risk of cervical cancer. Aberrant DNA methylation pattern may also be involved in development of cervical cancer [15].

Tumor extension

The pattern of local growth may be exophytic if cancer arises from the ectocervix or endophytic if it arises from the endocervical canal. Growth may be infiltrative or ulcerative lesion if necrosis accompanies the growth. Lymphatic drainage is into the paracervical and parametrial lymph nodes then through the cardinal ligament empty into ureteric nodes then flows into obturator and internal, external and common iliac lymph nodes and lyphatics from posterior cervix course through the rectal pillars and the uterosacral ligaments to the rectal lymph nodes. Presence of lymphovascular space invasion (LVSI) during deeper tumor invasion into the stroma, blood capillaries and lymphatic channels is regarded as poor prognostic indicator in early stage cancers. Local tumor extension can cause ureteral blockage (commonly), bladder invasion through vesicouterine ligaments, rectum involve late as it is separated from cervix by posterior cul de sac. Distance metastasis may occur through haematological spread to lungs, ovaries, liver and bone. There are some rare cervical cancers like-adenosquamous, adenoid cystic, adenoid basal epithelioma, glassy cell carcinoma, large cell and small cell neuroendocrine tumor of cervix, sarcomas and malignant lymphomas.

Diagnosis

Most of the patients are asymptomatic and diagnosed with abnormal Pap smear. Early stage cervical cancer will have watery discharge per vaginum usually blood tinged and intermittent vaginal bleeding following coitus or douching. Later there can be vaginal discomfort, malodorous discharge and dysuria. As malignancy advances may cause uncontrolled bleeding from tumor bed, pressure symptoms like lower extremity and low back pain, ureteral obstruction, hydronephrosis, uremia, hematuria and symptoms of vesicovaginal or rectovaginal fistula.

In early stage cervical cancer the physical findings may be normal. When the disease advances there may be enlarged supraclavicular or inguinal lymphadenopathy, lower extremity edema, ascites or decreased breath sound. Speculum examination and thorough vaginal and rectal examination will give the proper clinical staging. Lesions may appear as exophytic or endophytic growth; as a polypoid mass, papillary tissue, or barrel shaped cervix; as a cervical ulceration or granular mass; or as necrotic tissue with purulent or bloody discharge.

Differential diagnosis

Cervical leiomyoma, cervical polyp, prolapsing uterine sarcoma, vaginitis, cervical eversion, cervicitis, threatened abortion, placenta previa, cervical pregnancy, condyloma acuminata, herpetic ulcer and chancre. Primary melanoma, Paget's disease and vaginal cancer can also be differential diagnosis.

Clinical Approach

Screening with Papanicolaou (Pap) testing is the basic evaluation. If pap positive colposcopy and biopsies with further workup of cervical intraepithelial neoplasia (CIN), including excisional procedures should be done. If pathologic evaluation after loop electrosurgical excision or conisation suggests invasive cancer with positive margins then radical treatment should be done. Patients with suspicious or grossly abnormal cervical lesions on physical examination should undergo biopsy regardless of the cytologic findings. Once the diagnosis is made serum biochemical test for renal and liver function tests, complete blood count (CBC) including platelets, and imaging studies (optional for stages ≤ IB1) should be done for staging and surgical staging in early stage. Cystoscopy and proctoscopy should be performed in patients with bulky (≥ stage I B2) tumor to rule out local invasion of the bladder and the colon respectively. Barium enema studies can be used to evaluate extrinsic rectal compression from the cervical mass [3].

American society for colposcopy and cervical pathology (ASCCP) and American society for clinical pathology (ASCP) recommend screening guidelines as follows [16].

1. Screening recommended. From 21 years of age and not <21 years of age.
2. Pap smear should be done every 3 years in the age group 21-29 years.
3. HPV DNA test and cytology every 5 years (preferred) or cytology alone every 3 years (acceptable) is required in age group 30-65 years.
4. No screening recommended after65 years of age if adequate prior screening has been negative and high risk factor is not present.

After 65 years of age women who have positive HPV test may require continued screening. Women who had undergone a total hysterectomy may not require cervical cancer screening except after supracervical hysterectomy, hysterectomy for CIN 2/3 lesion treated in past 20 years or cervical cancer.

Women in whom HPV test is positive but Pap smear is negative should have follow-up every 12 month interval. Women with Pap smear report of atypical squamous cells of undetermined significance(ASCUS) but HPV test is negative then she can be rescreened in 5 years or with cytology alone screening in 3 years. Colposcopy is indicated if a women show positive HPV test.

MRI or PET scanning is better over CT scan for patients with stage 1B2 disease or higher to know metastasis in the body. Magnetic resonance whole-body diffusion weighted imaging can differentiate metastatic nodes from benign nodes [17].

Table 1: Staging of cervical cancer (FIGO staging 2010/NCCN guideline 2015).

Stage 1	Cervical cancer confined to cervix
Stage 1 A	Microscopic diagnosis of invasion from base of epithelium 5mm depth and 7mm horizontal spread or less. Vascular space involvement disregarded.
Stage1A1	Measured stromal invasion 3mm in depth or less and horizontal spread 7mm or less.
Stage 1A2	Measured stromal invasion 3-5mm in depth and horizontal spread 7mm or less.
Stage 1B	Clinically visible lesion confined to cervix or microscopic lesion >stage 1A2.
Stage !B1	Clinically visible lesion 4cm or less in greatest dimension.
Stage 1B2	Clinically visible lesion >4cm in greatest dimension.
Stage II	Cervical cancer invades beyond uterus but not upto pelvic wall or lower third of vagina.
Stage IIA	Tumor without parametrial invasion.
Stage IIA1	Clinically visible lesion 4cm or less in greatest dimension.
Stage IIA2	Clinically visible lesion >4cm in greatest dimension.
Stage IIB	Tumor with parametrial invasion.
Stage IIB1	Tumor involve lower third of vagina no involvement of parametrium.
Stage IIB2	Tumor with parametrium invasion.
Stage III	Cervical cancer invades beyond uterus upto pelvic wall and/ or lower third of vagina or causes hydronephrosis or non functional kidney.
Stage IIIA	Tumor involve lower third of vagina no extension to pelvic wall.
Stage IIIB	Tumor extends to pelvic wall and /or causes hydronephrosis or non functioning kidney.
Stage IVA	Tumor invades mucosa of bladder or rectum or extends beyond true pelvis.
Stage IVB	Distant metastasis (including peritoneal involvement, supraclavicular or mediastinal or paraaortic node involvement. Lung, liver or bone involvement.

Staging of cervical cancer usually done clinically and preferably confirmed with a bimanual pelvic examination under anaesthesia. FIGO staging in collaboration with who and the international Union against cancer (UICC) is followed worldwide [18,19] (Table 1).

Treatment

Treatment of cervical cancer is based on stage of the disease, age, fertility status, menopausal status of the patient and associated comorbid conditions and histology and cervical diameter. Treatment requires multidisciplinary approach involving a gynaecologic oncologist, radiation oncologist and medical oncologist [20].

Treatment of stage 1 cervical cancer

Nodal metastasis is 1% with stromal invasion <1 mm, stromal invasion 1-3 mm have 1.5% risk in stage IA1 cervical cancer. In Stage IA1 with LVSI, lymph node metastasis & cancer recurrence rate is 5%. Lymph node metastasis is 7% and risk of disease recurrence is 4% inStage 1A2 cancer.

IA1 with/without LVSI and 1A2 can be treated with Cone biopsy (cold knife cone preferred over LEEP) preferably a non-fragmented specimen of 3 mm negative margin. If margin of the cone comes negative and stage IA1 without LVSI and operable extrafascial hysterectomy to be done and if found non operable patient can be kept under observation and followed up by surveillance. If margins are positive and fertility desired Radical Trachelectomy to be performed with pelvic lymphnode dissection with/without para-aortic lymphnode sampling or sentinel lymphnode mapping done for stage IA1 with/without LVSI and 1A2 or repeat cone biopsy can be considered for more depth evaluation in stage IA1 without LVSI. If fertility not desired extrafascial (in IA1 without LVSI only) or modified radical hysterectomy (type2) & pelvic lymphadenectomy with or without para-aortic lymphnode sampling to be performed or sentinel lymph node mapping can be considered in patients to avoid long-term side effects of radiotherapy (RT)/patients hoping to retain ovarian function or pelvic RT with brachytherapy (total point A dose75-80 Gy) and surveillance to be done or repeat cone biopsy for more depth evaluation can be considered in stage IA1 without LVSI.

If fertility is desired: In stage IA2 and IB1 with lesion <2 cm diameter radical trachelectomy & pelvic lymphadenectomy (laparoscopic/open) can be performed [21]. High cure rates & successful pregnancies seen in young, low BMI patients with tumor <2 cm, no nodal involvement & tumor is not above internal os in MRI. Recurrence rates are similar to those of radical hysterectomy. In a radical trachelectomy cervix, vaginal margin and supporting ligaments removed leaving the uterus body and its attachments [22]. It can be performed by vaginal or abdominal route. In abdominal route parametrium resection can be done in better way but fertility conservation will be less [23]. Due to the aggressive nature of tumors of neuroendocrine histology or adenoma malignum are contraindicated for radical trachelectomy [24]. A case series involving 125 cervical cancer cases treated with vaginal radical trachelectomy reported 106 pregnancies among 58 patients [25]. A systematic review of 413 cervical cancer patients managed with abdominal radical trachelectomy. Out of 413,113 women attempted pregnancy and 67 women (59%) successfully conceived [26]. Miscarriage and preterm labor are found more commonly in these women who had radical trachelectomy [25,26].

Stage IB1 & IIA1 can be managed with modified radical hysterectomy & pelvic lymphadenectomy with or without para-aortic LN sampling and sentinel lymph node mapping can be considered or pelvic RT with brachytherapy (total point A dose80-85 Gy) with or without concurrent cisplatin containing chemotherapy (CCCT) can be used.

Stage IB2 & IIA2 Pelvic RT with concurrent cisplatin containing chemotherapy with brachytherapy (total point A dose ≥85 Gy), followed by surveillance Or radical hysterectomy with pelvic lymphadenectomy with or without para-aortic LN sampling and follow up can be done or Pelvic RT with concurrent cisplatin based chemotherapy with brachytherapy (point A dose75-80 Gy), adjuvant hysterectomy and surveillance can be done.

A randomized study compared RT alone vs. radical hysterectomy with lymphadenectomy for early stage cervical cancer (IB-IIA) and adjuvant RT was given to those with histopathological examination of parametrical extension, <3cm of uninvolved cervical stroma, positive margins or positive nodes. Similar outcomes were noted with radiation *vs.* surgery with or without postoperative RT. But complication rates were higher with combined surgery and RT therapy [27].

Table 2: Sedlis criteria for Negative nodes, negative margin and negative parametrium.

LVSI	Stromal invasion	Tumor size (cm) by clinical palpation
+	Deep1/3	any
+	Middle1/3	≥2
+	Superficial1/3	≥5
-	Deep/middle1/3	≥4

Surgical finding & adjuvant therapy in stage IB2 & IIA2- If in surgery nodes are negative, margin and parametrium negative patient can be kept under observation or she can be given pelvic RT if high risk factors (large primary tumor, deep stromal invasion or LVSI that meet Sedlis criteria (Table 2) with or without concurrent cisplatin based chemotherapy. If pelvic nodes &/or surgical margin &/or parametrium found positive pelvic RT with CCCT with or without vaginal brachytherapy can be given.

A GOG study compared adjuvant RT *vs.* no further treatment in a randomized trial of selected patients with node negative stage 1B carcinoma of cervix after surgery. At 2 year the recurrence free survival rate was 88% in adjuvant RT group *vs.* 79% no adjuvant RT group. After long term follow up till 12 years following adjuvant RT shows overall improved survival rate [28].

Para-aortic LN positive in surgical staging-chest CT/PET CT scan to be done. If negative distant metastasis Para-aortic node RT with concurrent cisplatin based chemotherapy with pelvic RT with or without brachytherapy is the treatment. If distant metastasis positive then biopsy from suspicious areas to be done**.** Patients with biopsy negative will manage as negative distant metastasis and if biopsy positive then manage with systemic therapy with or without individualized RT.

Sentinel lymphnode (SLN) mapping for cervical cancer

In gynecologic oncology practice SLN mapping as part of the surgical management of stage 1 cervical cancer is considered. This technique can be used in tumor upto 4cm size but best results are seen with <2cm size tumor [29]. In this technique dye or radio colloid technetium-99 (99 Tc) directly injected into the cervix at 2 point (3 and 9 o'clock) or 4 point (3, 6, 9, 12 o'clock) and the SLN are identified by direct visualization of colored dye during surgery. A florescent camera is required if indocyanin green dye is used or a gamma probe is required if 99Tc is used. Following a cervical injection SLN are commonly located medial to the external iliac vessels, ventral to the hypogastric vessels or in the superior part of the obturator space. SLN usually undergo ultrastaging by pathologist, which allows higher detection of micrometastasis that may alter the postoperative management of the patient [30].

The principle to be followed are- all mapped SLN (intracervical inj/99Tc /both) should be excised and submitted for ultra staging. If on ultrastaging H & E staining is negative, then any suspicious LN should be removed regardless of mapping. Side specific lymphadenectomy (including internal iliac or subaortic nodes) and parametrectomy is performed enbloc with a resection of the primary tumor if there is no mapping on a hemipelvis. In a meta-analysis of data from 1112 patients who were managed with SLN mapping showed detection rates of 92.2%, sensitivity of 88.8% and negative predictive value of 95 % [31]. The SENTICOL study demonstrated the utility of SLN mapping and showed that bilateral SLN biopsy is better than unilateral SLN biopsy in providing reliable assessment of sentinel node metastasis and fewer false negatives [32].

Role of minimally invasive surgical approaches for cancer cervix

Definitive comparison of safety and efficacy of open abdominal versus minimally invasive surgical techniques in the literature the data is insufficient [33]. Studies found that there are advantages of robotic and laparoscopic radical hysterectomy for cancer cervix like lesser duration of hospital stay and more rapid recovery [34]. Studies having 6 years of follow up following laparoscopic radical hysterectomy found that the recurrence rates are low [35,36]. The ongoing LACC phase III trial is comparing the disease free survival in more than 700 patients undergoing open radical hysterectomy, total laparoscopic radical hysterectomy/total robotic radical hysterectomy [37].

Stage IB2, IIA2, IIB, IIIA, IIIB, IVA can be managed with radiologic imaging or surgical staging with extraperitoneal/ laparoscopic lymphadenectomy. On imaging and on surgical staging if negative adenopathy then treatment with Pelvic RT with concurrent cisplatin based chemotherapy with brachytherapy is required**.** If on imaging positive adenopathy needle biopsy to be done. If pelvic LN positive and para-aortic LN negative then treatment with Pelvic RT with CCCT with brachytherapy with or without para-aortic RT/para-aortic LN dissection is done. If pelvic and para-aortic LN positive then extra peritoneal LN dissection to be done. If distant metastasis found treatment with systemic therapy with or without individualized RT can be done. If para-aortic LN negative treatment with Pelvic RT with CCCT with brachytherapy is given**.** If para-aortic LN positive treatment with extended field RT with brachytherapy and CCCT can be given. All the patient will be for Surveillance.

If on surgical staging Pelvic LN positive & para-aortic LN negative can be managed with pelvic RT with CCCT with brachytherapy. If para-aortic LN positive then imaging study as indicated clinically to rule out distant metastasis can be done. If negative distant metastasis, treat with pelvic and para-aortic RT with CCCT with brachytherapy. If distant metastasis positive then needle biopsy to be done. If needle biopsy positive systemic therapy with or without individualized RT required. Trials have shown that concurrent cisplatin based chemoradiation results in a 30-50% reduction of risk of death compared to RT alone in stage1B2-IV A cervical cancer [38].

Surveillance of treated patients done with:

1. Histopathological examination every 3-6m (every 3 months in High risk and every 6 months in low risk patients) for 2 year then every 6m for 3-5 year, then annual based on patients risk of disease recurrence.
2. Cervical/ vaginal cytology annually as indicated for lower genital tract dysplasia. (for those had fertility sparing surgery) [39].
3. Patient education regarding symptoms suggestive of disease recurrence (eg. Vaginal discharge, weight loss, anorexia, pain in the pelvis, hip, back or legs, persistent coughing) is recommended.

4. Patients should be counseled on lifestyle, nutrition, obesity, exercise, sexual health, vaginal lubricant or estrogen cream use. Cessation of smoking and abstinence should be encouraged [40].

5. Imaging is not routinely recommended for surveillance but may be indicated if the patient has symptoms or signs that are suspicious for recurrence Chest X-ray, CT/MRI/PET CT.

6. CBC, BUN creatinine as indicated clinically.

7. In patients at high risk for locoregional (central/para-aortic) failure a combined PET-CT scan or any other imaging test to be done 3-6 month after treatment for detecting early or asymptomatic disease that is potentially curable [41].

8. Use of vaginal dilator after RT to prevent or treat vaginal stenosis should start 2-4 weeks after completion of RT and can be performed indefinitely [42].

9. Cervical cancer survivors are at risk of developing radiation induced second cancers especially at radiated sites near cervix (eg. colon, rectum/anus, urinary bladder) and require careful surveillance [43].

Role of ovarian transposition

Ovarian failure in premenopausal women is possible following Pelvic RT or chemoradiation [44]. For women of less than 45 years of age with squamous cell cancers ovarian transposition may be considered to preserve her ovarian function [45].

Incidental finding of invasive cancer following simple hysterectomy

If after simple hysterectomy review of histopathology finding tumor is stage 1A1 without LVSI then only observation and surveillance can be done. If stage IA1 with LVSI or ≥stage 1A2, CBC, liver and renal function test, chest X-ray, CT/PETCT scan/MRI as indicated to be done. If margins negative and imaging negative then Pelvic RT with brachytherapy with or without CCCT or complete parametrectomy with upper vaginectomy, pelvic lymphadenectomy with or without para-aortic lymph node sampling to be done. If nodes found to be negative patient can be kept under observation but optional pelvic RT with or without vaginal brachytherapy is considered if they have high risk factors like large primary tumor, deep stromal invasion and/or LVSI [28]. If nodes found positive and/or positive surgical margin and/or positive parametrium then pelvic RT (para-aortic RT if para-aortic node positive) with CCCT with or without individualized brachytherapy (if positive vaginal margin) is the treatment. If surgical margins positive or gross residual disease and imaging negative for nodal disease then pelvic RT (para-aortic RT if positive) with CCCT with or without individualized brachytherapy (if positive vaginal margin) can be considered. If imaging positive for nodal disease then surgical debulking of bulky tumor followed by pelvic RT (para-aortic RT if positive) with CCCT with or without individualized brachytherapy (if positive vaginal margin) can be considered [20].

Persistent or recurrent disease

In women with stage IB-IIA cervical cancer with no lymphnode involvement, there is 10-20% recurrence chance and if lymphnode involved or advanced cancer the recurrence chance is upto 70% [46]. The majority of recurrence occurs within 2 years of diagnosis and the prognosis is poor. Recurrence should be proven by biopsy before proceeding for the repeat treatment. Repeat Imaging or surgical exploration to be done if indicated. Treatment is based on the performance status of the patient, the site of recurrence and or metastases, the extent of metastatic disease and prior treatment.

For Local/regional recurrence if patient not had Prior RT or failure outside RT field, surgical resection if feasible and Tumor directed RT with platinum based chemotherapy with or without brachytherapy. If again Recurrence Chemotherapy/palliative care.

For Local/regional recurrence if patient had Prior RT with central disease Pelvic exenteration with or without intraoperative RT(IORT) or Radical hysterectomy/brachytherapy if <2cm lesion and if again recurrence Chemotherapy/palliative care. If patient had Prior RT with non-central disease resection with IORT for close /+ve margin or tumor directed RT with chemotherapy or Chemotherapy or palliative care is required.

After treatment of relapse long term disease free survival rates of 40% have been reported [47]. Surgical mortality with pelvic exenteration procedures with or without IORT is ≤5% with survival rate upto 50% in selected patients [48]. Adequate rehabilitation programmers dealing with psychosocial or psychosexual consequences of these procedures is required.

Distant metastasis

If amenable to local treatment resection with/without RT or local ablative therapy with/without RT or RT with/without Concurrent chemotherapy followed by surveillance can be done. If tumor is not amenable to local treatment clinical trial/Chemotherapy/supportive care to be given.

Palliative care

Palliative chemotherapy is administered only if this treatment does not cause significant decline in patient's quality of life. Women with persistent nausea & vomiting from tumor-associated ileus may benefit from a gastrostomy tube. Urinary fistulas & bowel obstruction can be managed surgically. Pain management forms the basis of palliation.

Chemotherapy (for Recurrent or Metastatic Disease)

Combination chemotherapies:

1st line: Cisplatin/paclitaxel/bevasizumab, Cisplatin/Paclitaxel, Carboplatin/Paclitaxel, Cisplatin/Topotecan, Cisplatin/Gemcitabine, Topotecan/Paclitaxel, Topotecan/Paclitaxel/Bevasizumab [49,50]. Possible Second line therapy: Bevacizumab/Docetaxel/5FU/Gemcitabine/Iphosphamide/Irinotecan/Mitomycin/Topotecan/Pemetrexad/Vinoralbine.

First line single agent therapy: Cisplatin (preferred), Carboplatin, Paclitaxel [51].

A monoclonal antibody Bevacizumab binds to a protein called vascular endothelial growth factor (VEGF) and may prevent growth of new blood vessels of tumors. Patient receiving two drugs CCCT shows higher response rate and progression free survival (PFS) than

single agent cisplatin therapy [52]. Patients who received cisplatin/plactitaxel combination chemotherapy have significant improvement in quality of life. The regimens of cisplatin/paclitaxel or carboplatin/paclitaxel are less toxic and easier to administer.

A Cochrane review in 2010 analysed 18 trials to assess the effect of chemoradiation (with or without surgery) over only RT (with or without surgery) shows significant survival benefits. Chemoradiotherapy reduces local and distance recurrence/progression and improves disease free survival [53]. Another review in 2012 evaluated 368 women for the effectiveness and safety of platinum based chemotherapy after radical hysterectomy, radiotherapy or both in the treatment of early stage cervical cancer (IA2-IIA) shows chemoradiation may improve survival and is associated with an increased risk of severe acute toxicity [54].

A review evaluated the safety and effectiveness of adjuvant therapies (RT, chemotherapy followed by radiotherapy, chemoradiation) after radical hysterectomy, radiotherapy or both in the treatment of early stage cervical cancer (I B1, I B2 or IIA) in 397 women. The result was radiation decreases the risk of disease progression compared with no further treatment [55]. A Cochrane review included 1217 women to determine whether hysterectomy, in addition to standard treatment with radiation or chemotherapy or both, in women with locally advanced cervical cancer (Stage I B2 to III) is safe and effective compared with standard treatment alone shows insufficient evidence that these adjuvant therapies improves survival. However meta analysis of 571 patients neoadjuvant chemotherapy and hysterectomy vs. radiotherapy alone shows less death rates with neoadjuvant chemotherapy plus hysterectomy than those received radiotherapy alone [56].

A Cochrane review evaluated in 978 women the effect of adjuvant chemotherapy (ACT) after concurrent chemoradiation (CCRT) on survival of women with locally advanced cervical cancer compared with CCRT alone. It shows significant improvement in PFS and overall survival in women who were given CCRT plus ACT compared with those treated with CCRT alone [57].

Prognosis

In general 5-year survival rates are: more than 90% for stage-I, 60-80% for stage-II, around 50% for stage-III and less than 30% for stage-IV cancers. Leiomyosarcomas, neuroendocrine tumors of cervix and cervical stromal sarcomas are of very poor prognosis.

Management during Pregnancy

Cervical cancer is the most frequently diagnosed gynecological malignancy during pregnancy and stage 1 cancer common with better survival chance [58]. Invasive cervical cancer, require multidisciplinary care and the women has to take important decision to delay the treatment till fetal maturity or undergo immediate treatment depending on the stage of cancer [59]. No difference in survival seen between pregnant & non pregnant women with cervical cancer matched by age, stage, and year of diagnosis.

Stage I cervical cancer in pregnancy

Women with stage IA1 (3 mm/less) squamous cell cervical carcinoma & without LVSI may deliver vaginally & can be re-evaluated 6 weeks postpartum. In Stage IA/IB- there is no increase in maternal risk if treatment is intentionally delayed to optimize fetal maturity regardless of the trimester in which the cancer was diagnosed. Planned treatment delay for women who are ≥20 week's gestation who desire to continue their pregnancy is generally acceptable. Patients with early stage disease may prefer to undergo surgery- radical hysterectomy and node dissection instead of RT to avoid radiation fibrosis and to preserve their ovaries. Patients who delay treatment should undergo cesarean section with concurrent radical hysterectomy and pelvic node dissection. The protocols may need to be modified for those choosing RT with or without chemotherapy [60].

Advanced cervical cancer in pregnancy

If diagnosed prior to fetal viability are offered primary chemoradiation and spontaneous abortion of the fetus tends to follow whole-pelvis RT. If diagnosed after fetal viability and a delay until fetal pulmonary maturity is elected, then patient will have to accept an undefined risk of disease progression and a classical CS is performed followed by Chemoradiation is administered after uterine involution.

Role of uterine artery embolisation (UAE) in cervical cancer

UAE is a safe and effective flow directed, targeted, minimally invasive therapy for control of massive bleeding in cervical cancer and improves the patient's quality of life by reducing anemia without multiple blood transfusions as well as help them to be fit for next dose of CCRT or surgery [61]. Most common side effect of UAE is severe pain which can be managed with analgesics.

Prevention of HPV infection

Can be tried with the use of condom but it does not prevent transmission completely though it may reduce the chances of HPV infection [62]. A study in mouse found that carrageen an a polysaccharide present in some vaginal lubricants prevents infection [63]. HPV 16/18 vaccine found to be efficacious against CIN grade 2/3 and adenocarcinoma in situ as studied by Papilloma Trial against Cancer in young Adults (PATRICIA). Use of HPV 6/11/16/18 vaccine reduced the risk of any high grade cervical lesions by 19%. [64]. The Advisory Committee on Immunisation Practices (ACIP) recommends routine HPV vaccination of girls aged 11-12 years (as early as 9 years) with 3 doses of either HPV vaccine. In women who have not been previously vaccinated or who have not completed the full series catch up vaccination is recommended for females aged 13-26 years [65]. The ACIP also recommends routine use of quadrivalent HPV vaccine in boys aged 11-12 years, as well as in males aged 13-21 years and can be given up to 22-26 years [66]. Screening for cervical cancer should continue in vaccinated women, following same guidelines as in unvaccinated women. Oncogenic HPV types other than 16 and 18 accounts for 1/3rd of cases and cross protection by these vaccines may be only partial hence these vaccines do not provide complete protection against cervical cancer. The duration of protection with HPV vaccine is 6-8 years but whether revaccination will be necessary needs continuing follow up [67].

Immunomodulatory agents

Drugs reported to have apoptotic and immunomodulatory activities and are suitable for chemo immunotherapy include-Chemotherapeutic drugs (cyclophosphamide, doxorubicin and paclitaxel) Imiquimod and Gemcitabine. In patients with HPV-

associated cervical lesions, Doxorubicin can induce immunogenic cell death [68,69]. Imiquimod can activate Immune cells through TLR-7 and induces secretion of interferon-alpha (IFN-alpha), IL-6 and TNF-alpha [70]. Imiquimod in combination with E7 DNA vaccination can enhance antitumor immunity and increases the number of NK1.1 cells in the tumor microenvironment [71]. A pyrimidine nucleoside anti-metabolite, Gemcitabine (GEM), is a cytostatic agent with potent antitumor activity [72].

Cytokines therapy clinical trials in cervical cancer

The pathways that contribute to the uncontrolled growth of cancer cells can be interrupted by the cytokines due to their immunostimulatory properties and they prevent metastasis of cancer cells [73]. The cytokines that have been evaluated in clinical trials for cervical cancer are IL-2 and IL-12, granulocyte-macrophage colony stimulating factor (GM-CSF), and IFN-alpha [74]. The most effective cytokines used in clinical trials for cervical cancer treatment is IL-12,which has been used with naked DNA vaccine, viral gene therapy (adenovirus), ex vivo gene therapy, and in combination with E6 and E7 antigens [75,76].

Gene therapy clinical trials in cervical cancer

Cancer specific gene therapy are done by silencing specific target genes with application of SIRNA, those are noncoding RNAs 21-25 nucleotides in length that mimic endogenous micro RNAs and can effectively inhibit the translation of target MRNAS [77]. Disadvantage with use of synthetic SIRNA is of high cost. SIRNA can be produced by cloning of DNA inserts in a molecular vector [78]. The earlier studies on SIRNA against cervical cancer used chemically synthesized SIRNAs but subsequent studies used more efficient molecular vectors which inhibit expression of HPV oncogenes [79]. The other agents used for the release of siRNAs at the tumor site are biogels, combined with liposomes and chemotherapeutic drugs, and they are of greater efficiency [80].

Conclusion

With effective treatment the cure rate can be up to 80% in early stage diseases and up to 60% in advanced stage cervical cancers. HPV vaccine is a hope for prevention of cervical cancer and this may be the best way to improve mortality and morbidity from cervical cancer in near future. However the regular screening which has proved in developed countries in reducing cervical cancer is required to be implemented for all the women in developing countries.

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