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CARCINOMA CERVIX: CURRENT STATUS AND FUTURE PERSPECTIVE IN INDIA

Oncology

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ABSTRACT

In India about 14.5 lakhs of new cases are diagnosed and about 7.36 lakhs patients died with cancer in 2016. Cervical cancer is the fourth most common malignancy worldwide and second most common cancer diagnosed among women in India. Nearly all cases of cervical cancer resulted from human papilloma virus infection. Most of cases presented in advanced stage due to lack of awareness and low socioeconomic status. In this article we review the strong need of education, awareness about screening programs, HPV vaccination programme, advanced treatment techniques and new targeted therapeutic agents for prevention, early detection and better treatment outcome to reduce the morbidity and mortality associated with advanced stage.

KEYWORDS

Cervix cancer, Screening, HPV vaccination, Targeted therapy

Introduction

Now Cancer is the leading cause of death worldwide. In India about 14.5 lakhs of new cases are diagnosed and about 7.36 lakhs patients died with cancer in 2016 despite of increasing facility and advancement in cancer treatment. There is a prediction that incidence will increase to 17.3 lakhs by 2020.

Cervical cancer is the fourth most common malignancy worldwide and second most common cancer diagnosed among women in India. According to the World Health Organization (WHO) estimates, 5,28,000 new cases of carcinoma cervix were detected worldwide in 2012 with an estimated 2,66,000 deaths, accounting for 7.5% of all female cancer deaths. In India, annually, about 1,32000 new cervical cancer cases and 80,000 deaths occur, this account about one third of global burden of death from cervical cancer in 2010 [1]. The incidence rises in 30-34 years of age and peaks at 55-65 years, with a median age of 38 years (age 21-67 years)[2].

Cervical cancer is the one of the preventable cancer and has good prognosis if diagnosed in early stage. In India about 70% cases present in an advanced stage (stage III or IV)).As nearly all cases of cervical cancer result from human papilloma virus infection, thus with proper screening and vaccination, we can prevent and diagnose the cervical cancer at early stage.

Various risk factors involved in carcinoma* cervix*:

1. HPV infection: It is the most common cause. At least 50% of men and women acquire genital HPV infection during their lifetime. All sexually active women are infected with HPV at least once during their lifetime, and the highest prevalence is seen soon after the onset of sexual activities[3]. HR HPV (high risk human papilloma virus) types 16 and 18 infections are considered responsible for about 75-80 per cent of cervical cancer worldwide[4]. Low-risk (LR) HPV types 6 and 11 cause almost all cases of genital warts[5]. HPV infection generally asymptomatic that's why it remains for long latent period to develop into invasive carcinoma. Prevention of HPV would, therefore, reduce the incidence of cervical cancers as well as genital warts, along with the morbidity, mortality and costs associated with these diseases.
2. Sexual activities: Most common route of spread of HPV infection is through sexual contact, especially early onset sexual activity, multiple partners, high-risk sexual partners and failure to use condoms[6].
3. Compromised immune system: A weak immune system, as a result of HIV or by drugs causing suppression of immune response, places women at high risk for HPV infection and cervical cancer.
4. Teenage pregnancy: A first term pregnancy in women <17 years of age, doubles risk of cervical cancer later in life, as compared to women with first term pregnancy at age 25 and older.
5. Multiple pregnancies: Women with 3 or more pregnancies are at an increased risk due to hormonal changes or weak immune system during pregnancy.
6. Smoking is risk factor is thought to be following two conditions. (I) Smoking can weaken the immune system around the cells of the cervix, which makes it harder to both prevent and clear high-risk HPV infections. These persistent high-risk HPV infections could then develop into abnormalities in the cells of the cervix. (II)The chemicals found in cigarettes and tobacco can damage the DNA of the cervical cells, which may contribute to the development of abnormalities and cancer[7].
8. Oral contraceptives: Long-term use (>-5 years) increases risk of cervical cancer.
9 Family histories: Woman with mother/sister having cervical cancer has 2-3 times risk of developing cervical cancer than women without family history[8].
10. Dietary habits: A diet deficient in fruits, vegetables, as well as being overweight, increases risk of cervical cancer[9].
11 Diethylstilbestrol (DES) increases risk of adenocarcinoma in cervix, especially women whose mother exposed with DES during pregnancy.

***Management and recent advance in treatment*:**

Most common histologic type is squamous cell carcinoma comprises 90% of cases and others are adenocarcinoma, adenosquamous, neuroendocrine, clear cell carcinoma, sarcomas etc[10].

It mostly present as large polypoidal friable mass originating from ectocervix, sometimes as infiltrating and ulcerative lesions. The most common symptoms are postmenopausal bleeding, metrorrahagia (intermenstrual bleeding), menorrhagia and post coital bleeding per vaginum. Patient may present with obstructive symptoms, bowel obstruction, renal failure, bleeding per rectum, foul smell discharge in advanced stage.

Treatment of cervical cancer varies with stage of disease:

Stage 0 (carcinoma In situ) women who want to preserve fertility, for *ectocervical lesions*; loop electrosurgical excision procedure (LEEP)/ laser therapy or conization / cryotherapy is the treatment of choice. For *endocervical lesion*; laser/cold-knife conization can be recommended. These ablative procedures allow tissue for further pathological evaluation to rule out micro invasive disease .and patients required continued surveillance post treatment also. Total hysterectomy is the treatment of choice for women who has completed their family.

Stage IA1 cancer Treatment of choice is surgery. Total abdominal hysterectomy, radical hysterectomy, and conization are accepted procedures. Lymph node dissection is usually not required if depth of invasion is <3 mm with no lymphovascular space invasion. For fertility sparing either vaginal trachelectomy or abdominal trachelectomy is preferred. Sentinel lymph node mapping for pelvic and Para aortic lymph nodes[11].These patients require close follow-up, with cytology, colposcopy, and endocervical curettage. In patients with comorbidities, medical conditions precluding surgical resection can be successfully managed with radical radiation therapy.

StageIA2, IB-1, or IIA-1 cancer: Radical hysterectomy and bilateral pelvic lymphadenectomy is recommended .Those patient who are unfit for surgery and elderly patients radical radiotherapy is advised.

Stage IB-2 or IIA-2 cancer: Radical hysterectomy and bilateral pelvic lymphadenectomy is recommended .Those patient who are unfit for surgery and elderly patients radical concurrent chemo-radiotherapy is advised. Both surgery and radical radiotherapy is equally effective only differ in morbidity[12].

Stage IIB, III A or IIIB .Radical radiotherapy concurrent with cisplatin is the treatment of choice, results from many large radomomized controlled trials show survival benefit[13-15].Patients with renal compromise concurrent carboplatin and paclitaxel can be given.

Stage IVA / IVB: Palliative radiation can be given for bleeding, pain, obstructive features. In selected patient with good performance status radical concurrent chemo radiotherapy or neo adjuvant chemotherapy followed by concurrent chemo radiotherapy can be offered. Cisplatin and paclitaxel is the most effective agent in carcinoma cervix. A recent phase III trial assessed four cisplatin-doublet regimens.

(Cisplatin–paclitaxel, cisplatin–topotecan, cisplatin–gemcitabine, and cisplatin–vinorelbine). No significant differences in overall survival. A combination with carboplatin –paclitaxel is preferred then cisplatin in term of less toxicity profile[16]. The NCCN also recommends docetaxel, gemcitabine, ifosfamide, 5-fluorouracil, mitomycin, irinotecan, and topotecan as possible candidates for second-line therapy (category 2B recommendation), as well as pemetrexed and vinorelbine (category 3 recommendation). Targeted agent like anti VEGF (bevacizumab, azpopanib) and anti EGFR (Cetuximab, erlotinib, gefitinib) are also emerging with limited benefit in locally advanced and recurrent/ metastatic disease.

Indication of adjuvant radiation therapy after radical surgery: *High risk*: pelvic lymph node metastasis, positive surgical margin, parametrial extension adjuvant chemo-radiotherapy is preferred [17].*Intermediate risk*: Deep cervical stromal invasion, lymphovascular space invasion: only adjuvant radiation therapy. *Low risk*: All other patients: No adjuvant therapy recommended.

The treatment should be completed within 8 weeks combined external beam radiotherapy and brachytherapy. Prolongation of treatment duration reduces the local control and survival of patients approximately 1%per day[18].

Doses in radical radiation therapy: External-beam pelvic irradiation combined with intracavitory applications to a total dose of 80Gy-85Gy to point A. External beam radiotherapy conventionally planned with four field isocentric technique with customized shielding to a dose of 45Gy to 50Gy at 1.8-2Gy/fraction. Some Institution give10Gy/5fr with mid line shielding after 40Gy/22fr by four fields to minimize toxicity to bladder and rectum. Now there are many newer techniques that gives more conformal dose distribution and reduce normal organ toxicity is preferred like 3D-CRT, IMRT, IGRT.

Brachytherapy: Brachytherapy is the essential component with external beam radiotherapy in locally advanced carcinoma cervix (Ib2-IVA) and brachytherapy alone can also be given in early stage(IA-IB1).High dose rate(HDR) and low dose rate (LDR) brachytherapy both are biologically equivalent and no difference in survival[19] but widely used is high dose rate brachytherapy as it is outpatient procedure, avoidance of radiation exposure to staff, reproducible applicator positioning, dose optimization with variable dwell time stepping. American brachytherapy society (ABS) recommend total dose of 80Gy-90Gy to point A in locally advanced carcinoma cervix. Traditionally dose in intracavitary brachytherapy is measured as per International Commission on Radiation Units and Measurements (ICRU) reference points. Point A is empiric point and does not reflect the exact dose to tumor and also points for bladder and rectum as dose is estimated on 2D orthogonal images.

In the recent year with availability of software of 3D planning of brachytherapy, there is volumetric assessment of dose can be measured. Planning with *Image guided brachytherapy (IGBT)* further can escalate the tumor dose and minimize the toxicity to organ at risk. Point A dose is equivalent to high risk clinical target volume(HR-CTV) and for bladder and rectum maximum irradiated 2cc of volume is measured as per recommendations by GEC-ESTRO and Image guided brachytherapy working group (IGBWG)[20-22].

5-year survival rate for people with stage 0 is about 93%,stage I 93%,stage IB 80%, stage IIA 63%,stage IIB 58%,IIIA 35%,IIIB 32%.IVA 16%,IVB 15%. Stage-wise recurrence rate: FIGO stage IB-10%, for stage IIA - 17%, stage IIB- 23%, and stages III and IVA - 42% and 74% respectively. The reported recurrence rate by tumor size is: tumors <2 cm 1.2% while for tumors >2 cm 21% (17). Most common sites of pelvic recurrence are cervix, uterus, vagina, parametrium, bladder, ureters, rectum, and ovaries. Most frequent distant sites are Para aortic lymph nodes (81%), lungs (21%), and supraclavicular lymph nodes (7%), and incidence relates with stage of disease.

Strategies for prevention and early detection of cervical cancer: Prevention can be done at three levels. Primary Prevention by preventing the initial onset of cervical cancer (by vaccination) and Secondary Prevention by early detection with screening and treatment of precancerous cervical lesions, Tertiary Prevention is treatment of cervical cancer to reduce morbidity and mortality, and improve Quality of Life.

In last few years incidence of cervical cancer is decreasing due to awareness and screening programme for women. In women attending cervical screening, seven out of ten (70%) can be protected from developing cervical cancer and others can be diagnosed at early stage and treated effectively.

Screening guidelines:

	ACS/ASCCP/ASCP	USPSTF
When to start	Age 21	Age 21
Intervals	Ages 21-29: Cytology alone every 3 years Ages 30-65: HPV and cytology "co-testing" every 5 years is preferred OR Cytology alone every 3 years is acceptable	Ages 21-29 years: Cytology alone every 3 years. Ages 30-65: HPV and cytology "co-testing" every 5 years for women who want to extend their screening interval OR Cytology alone every 3 years
When to stop	Women older than age 65 following adequate negative prior screening (Women with a history of CIN2 or a more severe diagnosis should continue routine screening for at least 20 years after diagnosis.)	Women older than age 65 who have had adequate negative prior screening (as defined below) and who are not otherwise at high risk (Adequate negative prior screening is defined as 3 consecutive negative cytology results or 2 negative co-tests within 10 years before cessation of screening, with the most recent occurring in the past 5 years.)
Post Total Hysterectomy	Women who have had a total hysterectomy (with removal of the cervix) should not be screened unless there is a history of CIN2 or more severe diagnosis in the past 20 years, or a history of cervical cancer ever	Women who have had a total hysterectomy (with removal of the cervix) should not be screened unless there is a history of high-grade precancerous lesion or cervical cancer

Compares current (2012) recommendations of two different groups: the U.S. Preventive Services Task Force (USPSTF) and multidisciplinary partnership among American Cancer Society/American Society for Colposcopy and Cervical Pathology/American Society for Clinical Pathology (ACS/ASCCP/ASCP) for screening of cervical cancer.

HPV Vaccination:

There are two HPV vaccines, namely Gardasil (MSD Merck) and Cervarix (GlaxoSmithKline Biologicals) approved by the USFDA (US Food and Drug Administration) are available for vaccination of adolescent girls. Gardasil is a quadrivalent vaccine (HPV 6, 11, 16, 18) and Cervarix is bivalent vaccine (HPV 16, 18). Prophylactic HPV vaccination can reduce the burden of cervical cancer in India by more than 75 per cent as per the study by Basu *et al*[23].

We usually give vaccine in 9-26 year age group. But early vaccination is more beneficial as adolescent girls are more vulnerable to HPV infection. 2 dose vaccination schedule is enough in 9-14 year of age but in girls more than 14 year, 3 dose vaccination schedule should be followed.

We can give it upto 45 year of age (catch up vaccination) which can provide some benefit. For this we use quadrivalent vaccine which has better coverage.

In India inclusion of HPV vaccine in national immunization programme is still controversial. Delhi has become the first state in the country to launch the Human Papillomavirus (HPV) vaccine as a public health programme for school children specially targeting girls studying in class VI, as declared by health minister Mr. Satyendar Jain in the international workshop for cancer awareness, prevention, screening and early detection for SAARC nations organized by Delhi State Cancer Institute in Feb-March 2016 under the guidance of Dr. R.K.Grover. As per WHO recommendations, the first dose of the vaccine should be administered to girls between 9 and 13 years. “But this would amount to almost 10 lakh girls in Delhi, which would not be practical in the first year. So we began by targeting only girls in Class VI. First phase has been started in august 2016.The another state in the country to launch HPV vaccine in the districts of Bathinda and Mansa by Principal Secretary Health, Mrs.Vini Mahajan on 23 November 2016, with technical support from WHO Country Office for India. Even after HPV vaccination women should go for routine screening by pap smear as vaccination can't replace routine screening method for early diagnosis.

Conclusion:

In Indian scenario cervical cancer is one of the most common cancers and presented in advanced stage due to lack of awareness and low socioeconomic status. There is strong need of increase education and screening programs to detect cancer in early stage and reduce the morbidity and mortality associated with advanced stage. The development of targeted therapies that selectively target specific molecular pathways involved in tumorigenesis may lead to other major advances in the management of cervical cancer. The role of immunotherapy is a promising and exciting new area of research that can potentially lead to further advancements in the treatment of locally advanced, recurrent, or metastatic cervical cancer. Development of the immune checkpoint blockade PD-1 and CTLA-4 inhibitors has shown promise and will need to be further studied as a means to achieve a durable response in cervical cancer.

Bibliography

1. Globacon 2012.Available from: http://www. Globacon. iarc.fr
2. Singh N.2005; HPV and Cervical cancer - prospects for prevention through vaccination. Indian J Med Paediatr Oncol. 26(1):20–23.
3. ICO Information Centre on HPV and cancer. Human Papillomavirus and Related Diseases in India (Report 2017); 2017.
4. Clifford G, Francheschi S, Diaz M, Munoz N, Villa LL.2006; HPV type-distribution in women with and without cervical neoplastic diseases. Vaccine.24 (Suppl 3):26–34.
5. Cancer Research UK, 2014. Cervical cancer risks and causes: The pill: Accessed: 19.07.2016.
6. Comparison of risk factors for invasive squamous cell carcinoma and adenocarcinoma of the cervix: Collaborative reanalysis of data on 8097 women with squamous cell carcinoma and 1374 women with adenocarcinoma from 12 epidemiological studies.2007; Int J Cancer :120:885-891.
7. Roura E et al, 2014. Smoking as a major risk factor for cervical cancer and pre-cancer: Results from the EPIC cohort. International Journal of Cancer 135, 453–466.
8. Frumovitz M.2013; Invasive cervical cancer: Epidemiology, risk factors, clinical manifestations, and diagnosis.
9. American Cancer Society (ACS). (2014, Jan. - Last revised).Cervical cancer: detailed guide.
10. Howlader N, Noone AM, Krapcho M, Garshell J, Miller D, et al. SEER cancer statistics review, 1975-2012., National Cancer Institute, Bethesda, MD, based on November 2013 SEER data submission, posted to the SEER web site, April 2014
11. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Cervical Cancer Version 1.2018.
12. Landoni F, Maneo A, Colombo A, Placa F, Milani R, et al.1997; Randomized study of radical surgery versus radiotherapy for stage Ib-IIa cervical cancer. Lancet. 350: 535–540
13. Morris M, Eifel PJ, Lu J, et al.1999; Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. N Engl J Med.340 (15):1137-1143. 35.
14. Rose PG, Bundy BN, Watkins EB, et al.1999; Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. N Engl J Med.340 (15):1144-1153. 36.
15. Keys HM, Bundy BN, Stehman FB, et al.1999; Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. N Engl J Med.340 (15):1154-1161.
16. Moore KN, Herzog TJ, Lewin S, Giuntoli RL, Armstrong DK, et al.2007; A comparison of cisplatin/ paclitaxel and carboplatin/paclitaxel in stage IVB, recurrent or persistent cervical cancer. Gynecol Oncol.105: 299-303.
17. Sedlis A, Bundy BN, Rotman MZ, Lentz SS, Muderspach LI, et al.1999; A randomized trial of pelvic radiation therapy versus no further therapy in selected patients with stage IB carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy: A Gynecologic Oncology Group Study. Gynecol Oncol.73: 177-183
18. Perez CA, Grigsby PW, Castro Vita H.et al: 1995; Carcinoma of uterine cervix, impact of prolongation of overall treatment time and timing of brachytherapy on outcome of radiation therapy.Int J.Radiol Oncol.Biol.Phys.32:1275-1288.
19. Patel FD, Sharma SC, Negi PS et al.1994; Low dose rate v/s High dose rate brachytherapy in the treatment of carcinoma cervix: A clinical trial, Int. J. Radiol. Oncol. Biol.Phys. 28:335-341.
20. Recommendation from Gynecological (GYN) GEC-ESTRO Working group (I); concept and terms in 3D image based 3D treatment planning in cervix brachytherapy with emphasis on MRI assessment of GTV and CTV: Radiotherapy and Oncology 2005, 74,235-245.
21. Recommendation from Gynecological (GYN) GEC-ESTRO Working group(II); concept and terms in 3D image based treatment planning in cervix brachytherapy – 3D volume parameters and aspects of 3D image based anatomy, radiation physics, radio biology : Radiotherapy and Oncology 2006,78,67-77.
22. Nag et al: 2004; Proposed guideline for image based intracavitary brachytherapy for cervical carcinoma: Report from image guided brachytherapy working group: Int. J.Radiation Oncology Biol.Phys. (60)4, 1160-1172.
23. Basu P, Roy chowdhury S, Bafna UD, Chaudhury S, Kothari S, Sekhon R, et al.2009; Human papillomavirus genotype distribution in cervical cancer in India: results from a multi-center study. Asian Pac J Cancer Prev.10:27–34.