



e-Newsletter

ISCCP

Member International Federation of Cervical Pathology and Colposcopy

Newsletter of Indian Society of Colposcopy & Cervical Pathology (Reg.)

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From the Editor's Pen

Dear Friends,

A VERY HAPPY NEW YEAR TO ALL! Hope you have a wonderful time ushering the New Year with your family and friends!

Welcome to the next edition of the Indian Society for Colposcopy and Cervical Pathology (ISCCP) newsletter for the year. We hope to bring the recent updates and trends in the field of cancer cervix and Colposcopy from places in India.

This issue has focuses on informative updates in the field of cervical cancer prevention and treatment. There are also reports on awareness drives and education of both the gynaecologists and the common people.

We are happy to announce that the next annual conference of ISCCP will be held at Bengaluru on 10th and 11th March 2018. Tentative program and registration form is also included. Register early to avoid disappointment. It is a nice opportunity for the members to deliberate on a series of latest developments in the field. We request that you people attend in large numbers and make the event a huge success!

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Announcement

All life members of ISCCP are requested to pay Rs 2,000/-to retain their membership of International Federation of Cervical Pathology and Colposcopy for 5 years. Cheques in favor ISCCP may be sent to:

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Forthcoming Conference

ISCCP Annual Conference

at Bengaluru on

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Awareness and Perceptions Regarding Common Cancers Among Women and Girls in India. Can it be prevented?

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Introduction:

The Centre for Interdisciplinary Research in Basic Sciences (CIRBSc.) at Jamia Millia Islamia, organized an Awareness Program entitled **“Awareness and perceptions regarding common cancers among women and girls in India. Can it be prevented?”** on September 28, 2017 in collaboration with Bio-Services | Prevention and Disease Control, Public Engagement Activities, Health Education and Research (<http://www.bio-services.org/>).

Background:

Cervical cancer is the fourth most common cancer affecting women worldwide¹. India alone accounts for one-quarter of the worldwide cervical cancer burden². The Human Papillomavirus (HPV) is considered as one of the major etiological factors for cervical cancer along with other factors³.

Screening for cervical cancer with the Pap smear test has become a widely accepted diagnostic tool⁴. Other than that, two vaccines, a quadrivalent ‘Gardasil’ (against HPV types 16, 18, 6 and 11) and a bivalent ‘Cervarix’ (against HPV types 16 and 18) were introduced for vaccinating young adolescent girls between ages 9–13 and/or 13–26-year young adults for purposes of primary prevention⁵.

Along with screening and vaccination, creating knowledge and awareness among youth can help reduce the cervical cancer burden further in the Indian population.

Objective:

To increase awareness and change existing perceptions regarding the commonly occurring “cervical cancer” among women and girls in India.

Method:

A questionnaire-based survey was conducted before and after the aforementioned awareness session in a total of 104 candidates which included graduates (B. Sc.), postgraduates (M. Sc.) and Ph. D students in the age group of 18–35 years comprising 59 girls and 45 boys.

The questionnaire developed for the participants consisted of the following questions:

1. Do you know that cervical cancer is the most common cancer in Indian women? Y / N
2. What is the principal cause of cervical cancer?
.....
3. Have you heard about the human papillomavirus (HPV)? Y / N
4. Is there any relation between HPV and cervical cancer? Y / N
5. If yes then, which are the oncogenic or cancer-causing HPV types?
6. Do you know that HPV can cause genital warts? Y / N
7. Are you aware of the existence of HPV vaccines? Y / N
8. Do you know the names of the vaccines?
9. Do you know who are eligible for HPV vaccination? ..
.....
10. Do you think all young girls should take the HPV vaccine? Y / N
11. Have you taken HPV vaccine? Y / N

All participants were requested to complete a 11-point questionnaire regarding cervical cancer, screening, vaccination and cancer-causing HPV types, and the answers were then analyzed before starting the lecture and after completion of lecture.

Results:

It was concluded on the basis of the questionnaire that out of 104, none of the students had taken HPV vaccine and out of the 59 girls none was either screened or vaccinated. The overall knowledge about oncogenic or cancer-causing HPV types, screening and vaccination was poor. Interestingly, most of the students however knew that cervical cancer is most common cancer in Indian women and HPV is the main causative agent for developing cervical cancer.

Before the awareness session, most of the participating

girls were not sure about whether all young girls should take HPV vaccine. However after the session all students agreed that young girls should get vaccinated against HPV. Information regarding the eligibility, dosage, schedule and cost of the HPV vaccines was lacking in a majority of participants although a few of them knew about FDA approved HPV vaccines available in India.

Conclusion:

Cervical cancer screening and HPV vaccination awareness among graduates (B. Sc.), postgraduates (M. Sc.) and Ph. D students was poor in both girls and boys. Regular public engagement activities related to health education is the need of the hour to maximize public awareness for cervical cancer prevention and control. It is suggested that there is a need for educational intervention and awareness campaigns to raise knowledge, change attitude and practices in order to prevent cervical cancer in India.

References:

1. International Agency for Research on Cancer (IARC), World Health Organization (WHO). GLOBOCAN 2012: estimated cancer incidence, mortality and prevalence worldwide in 2012: cancer fact sheets: cervical cancer. Lyon: IARC; 2014.
2. Ferlay J, Soerjomataram I, Ervik M, Forman D, Bray F, Dixit R. GLOBOCAN 2012, Cancer Incidence and Mortality Worldwide in 2012. Lyon, France: International Agency for Research on Cancer; 2012.
3. Neyaz MK, Hussain S, Hassan MI, Das BC, Husain Bharadwaj M. Novel missense mutation in FHIT gene: interpreting the effect in HPV-mediated cervical cancer in Indian women. Mol Cell Biochem. 2010; 335:53–58.
4. Franco EL, Harper DM. Vaccination against human papillomavirus infection: A new paradigm in cervical cancer control. Vaccine 2005; 23(17–18):2388–94.
5. Markowitz LE, Dunne EF, Saraiya M, Lawson HW, Chesson H, Unger ER, et al. Quadrivalent Human Papillomavirus Vaccine: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2007; 56: 1–24. Available: <http://www.ncbi.nlm.nih.gov/pubmed/17380109>.

Newer Modalities for Screening of Cervical Cancer

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Worldwide, cervical cancer is both the fourth-most common cause of cancer and the fourth-most common cause of death from cancer in women.

The newer modalities for screening of cervical cancer are as follows:

1. Fabric-based endocervical curettage: this new device (fig 1) uses a fabric hook, such as the hooks found on the rough side of Velcro, to do the sampling instead of the standard metal scraping device. The hook simultaneously biopsies, traps, and stores the tissue for transport to the lab.

A recent study¹ compared evaluated its use in physician and nurse colposcopists who switched from the old-school metal version of endocervical curettage (January 2010-July 2011) to the new fabric-based version (September 2011-October 2013). It found that the new fabric devices had significantly fewer 'inadequate' specimens -- meaning, patients did not need to return for repeat biopsies, translating to increased patient satisfaction. This device is not sharp and removes the appropriate amount of cells while minimizing discomfort. When applied to tissue with pressure, the fabric hook flexes downward exposing the hook tip to the tissue face

when rotated or agitated on the tissue surface. A colposcopist clinician is not required to handle the specimen and clean biopsy devices, thus reducing the risk of contamination. Its advantage is the ability to evaluate the inside of the cervix with ease.



Fig 1: Fabric based device vs. traditional curette

2. ZedScan spectroscopy: The ZedScan (fig 2) uses electrical impedance spectroscopy to detect pre-cancerous and cancerous cells in the cervix of women who have suspected cervical intra-epithelial neoplasia. It is a diagnostic tool intended as an adjunct to colposcopy in women who are referred

for colposcopy because of an abnormal cervical cytology result. It comprises of

- a handset used to examine the cervix a docking station used to charge the handset and connect it to a computer
- a single-use electrical impedance spectroscopy (EIS) sensor that fits over the snout of the handset for examinations.
- a software application for processing and storing information from the handset.

The ZedScan works by applying small alternating current at different frequencies to the cells lining the cervix and measuring the resulting voltage. The electrical resistance can be calculated to show the electrical impedance spectrum of the surrounding tissue. Healthy cervical epithelial tissue has a different impedance spectrum to abnormal tissue found in cervical intra-epithelial neoplasia (CIN). The ZedScan software analyses the impedance spectral data using a proprietary algorithm, and gives a value to indicate the likelihood that high-grade CIN is present. During the colposcopy, a series of 10–12 readings are taken from points evenly spaced around the transformation zone. The exact number of readings will depend on the size of the transformation zone, but at least 10 readings should be taken to ensure adequate coverage. To ensure that readings are taken from the right places around the transformation zone, the ZedScan handset displays a diagram of the measurement zone. This uses coloured dots to indicate the location and status of each measurement point. The colour of the dot indicates the result of the analysis:

- clear/white – no reading,
- green – high-grade CIN is unlikely to be present,
- amber – high-grade CIN is likely to be present,
- red – the highest likelihood that high-grade CIN is present.

The treatment recommendations would depend on the results of the ZedScan, the colposcopic examination and the original cytology result. However, it is intended only as an adjunct to colposcopy in patient assessment. It should not be used alone as a diagnostic tool or to decide on treatment. It must be used in conjunction with other

methods of assessing clinical signs and symptoms. A study² found that the use of an electrical impedance spectroscopic device increases detection of CIN2+ irrespective of hrHPV genotype.



Fig 2: ZedScan device

3. Gynocular Colposcope: It is a mobile colposcope with a replaceable and rechargeable battery. It can be hand held or used with a monopod or a tripod. It has been clinically tested in Sweden, Bangladesh, India and Uganda and is US FDA approved. The Gynocular can also be used together with Gynocular Triage to Diagnose (T2D) software, which is a secure, smart and user-friendly software for smartphones and desktops. The T2D enables to record patient data, review, refer patients, consult, teach and confer colleagues. T2D is FDA approved for use with the Gynocular. Its advantages are reduced cost as compared to a traditional colposcope, mirroring capabilities to desktop, laptop or screen, mobile with high quality optics and can also be a video-colposcope. It is lightweight (480g) and easily fits into a pocket or a small bag.



Fig 3: Gynocular colposcope

References:

1. Diedrich JT1, Rathore S, Bentz JS. Comparison of Tissue Yield Using Frictional Fabric Brush Versus Sharp Curettage For Endocervical Curettage. *J Low Genit Tract Dis.* 2017 Oct; 21(4): 304-306
2. Abdul S, Brown BH, Milnes P, Tidy JA. The use of electrical impedance spectroscopy in the detection of cervical intraepithelial neoplasia. *Int J Gyn Cancer* 2006; 16(5): 1823–32

HPV Vaccination: Current Scenario

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Introduction:

Cervical cancer is one among the preventable cancers that still is a leading cause of female cancer deaths in India¹. More than 85% of cervical cancer cases are diagnosed at the advanced stages of disease due to lack of population based screening system. Though the etiology of cervical cancer is multi-factorial, Persistent infections with carcinogenic human papillomavirus (HPV) types 16 & 18 are known to be responsible for 70% of all cervical cancer².

Types of HPV:

HPV infections are more than 200 types. HPV infection can be categorized as low-risk and high-risk types. Low risk types like 6, 11 etc usually are responsible for genital and anal skin warts. High risk types are responsible for carcinomas.

However, not all high risk types are carcinogenic. Generally, HPV infection gets cleared from women's system on its own within a year or two. Mostly persistent infection with high risk HPV types leads to dysplastic changes in the cervix which if not treated, over years undergo carcinogenic transformation.

Mode of spread and symptoms of HPV infection:

HPV infection is transmitted sexually (in both hetero and homosexuals). This is common among people with multiple partners. Mostly, women infected with HPV infection are asymptomatic.

Prevention:

Cervical cancer caused due to HPV infection is preventable by combined methods of primary and secondary prevention (vaccination and routine screening). Globally, many countries have HPV vaccination in their national immunization programmes.

There are 3 types of vaccines available globally. Cervarix, a bivalent vaccine which prevents HPV16,18 infection, Gardasil, a quadrivalent vaccine that prevents HPV 16,18, 6 & 11 infection and Gardasil9, a nonavalent vaccine prevents HPV 31,33,45,52&58 infection in addition to the coverage of quadrivalent type.

However, HPV vaccines neither provide protection against other sexually transmitted diseases nor previously infected HPV types. Since the vaccines available do not cover all types of carcinogenic HPV

types, the vaccinated women are recommended to undergo routine cervical cancer screening.

Immunogenicity & mode of action:

HPV vaccines are administered intramuscularly. WHO revised three dose schedules to 2 dose based on the efficacy data and 2 doses were proved non-inferior. The target population recommended is girls of age group 9-13 years. The doses are given with interval not more than 12-15 months³⁻⁶, post-vaccination, more than 99% of the individuals are sero-converted⁷⁻¹⁰. The virus like particle (VLP), a component of surface protein of HPV virus in the vaccine lacks viral DNA. Hence they are non-pathogenic & non-infectious. After vaccination, the VLPs are recognized by the immune system and antibody responses are generated. The concentration is 1-4 logs greater than the antibody levels induced by natural HPV infection. Hence it protects from infection each time when the body is challenged by exposure to the HPV virus.

Adverse effects:

Like most of the vaccines, post HPV vaccination, pain in the injection site was observed in clinical trials. Though adverse reactions like syncope, anaphylaxis, pregnancy loss and thrombo-embolism were reported in various clinical trials, The Global Advisory Committee on Vaccine Safety (GACVS) in 2014 -15³⁻⁵ reported that there was no evidence of association with these adverse effects and emphasizes on the safety of vaccine.

Current scenario in India:

Currently, bivalent and quadrivalent HPV vaccines are available in our country for use. The vaccine was in use only in private health care sectors. In October 2014, WHO recommended implementation of HPV vaccination along with comprehensive cervical cancer screening in programmatic conditions in India.

Delhi state is a pioneer in introducing the HPV vaccination in immunization schedule. In November 2016, the state offered school children of age group 11-13 to get vaccinated with HPV vaccine. Till March 2017 no serious adverse reactions were reported and 1,200 doses were administered¹¹.

Following this, Punjab also introduced HPV vaccination in the immunization schedule for school girls from class 6 in government sector of Bathinda and Mansa

districts in November 2016. As a result, in phase I, more than 97% of girls were vaccinated. Though few minor adverse events were reported, it was resolved locally¹². Both the states are planning to extend the vaccination programme and are due for 2nd dose.

References:

1. GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012. India Cancer Cervix Incidence and Mortality Estimates Lyon; 2012.
2. Forman D1, de Martel C, Lacey CJ, Soerjomataram I, Lortet-Tieulent J, Bruni L, Vignat J, Ferlay J, Bray F, Plummer M, Franceschi S. Global burden of human papillomavirus and related diseases. *Vaccine*. 2012 Nov 20;30 Suppl 5: F12-23. doi: 10.1016/j.vaccine.2012.07.055
3. World Health Organization. GACVS Safety Update on HPV Vaccines, Geneva 17 December, 2013.
4. World Health Organization. Global Advisory Committee on Vaccine Safety, Statement on the Continued Safety of HPV Vaccination. Geneva: WHO; 2014.
5. World Health Organization. Global Advisory Committee on Vaccine Safety, Statement on Safety of HPV Vaccines: 17 December, 2015. Geneva: WHO; 2015.
6. Human papillomavirus vaccines: WHO position paper, October 2014. *Wkly Epidemiol Rec* 2014; 89: 465-91.
7. Block SL, Nolan T, Sattler C, Barr E, Giacoletti KE, Marchant CD, et al. Comparison of the immunogenicity and reactogenicity of a prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in male and female adolescents and young adult women. *Pediatrics* 2006; 118: 2135-45.
8. Einstein MH, Baron M, Levin MJ, Chatterjee A, Edwards RP, Zepp F, et al. Comparison of the immunogenicity and safety of Cervarix and Gardasil human papillomavirus (HPV) cervical cancer vaccines in healthy women aged 18-45 years. *Hum Vaccin* 2009; 5: 705-19.
9. Zhu FC, Chen W, Hu YM, Hong Y, Li J, Zhang X, et al. Efficacy, immunogenicity and safety of the HPV-16/18 AS04-adjuvanted vaccine in healthy Chinese women aged 18-25 years: Results from a randomized controlled trial. *Int J Cancer* 2014; 135 : 2612-22.
10. Sankaranarayanan R, Prabhu PR, Pawlita M, Gheit T, Bhatla N, Muwonge R, et al. Immunogenicity and HPV infection after one, two, and three doses of quadrivalent HPV vaccine in girls in India: A multicentre prospective cohort study. *Lancet Oncol* 2016; 17: 67-77.
11. Chatterjee P: Delhi first state to launch HPV vaccine as public health programme in schools. <http://indianexpress.com/article/cities/delhi/delhi-first-state-to-launch-hpv-vaccine-as-public-healthprogramme-in-schools>
12. WHO: Punjab launches HPV vaccine with WHO support. http://www.searo.who.int/india/mediacentre/events/2016/Punjab_HPV_vaccine/en/

Update on Cervical Carcinoma Treatment

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Introduction

Cancers in women, including cervical, breast and ovarian cancer is responsible for thousands of mortalities among women. Cervical carcinoma is the third most common cause of cancer in women in the world¹. Mortality from cervical cancer in women among high-income countries have been reduced significantly after the introduction of cytology-based programs but this rate remains high in low and middle-income countries. The main causative agent associated with the development of cervical cancer is the human papillomavirus (HPV). HPV is seen in almost 99% of cases and vaccines can prevent its sexual transmission².

Cure rate in early stage (localized and regional) cervical cancer is approximately 60-90% with the available current treatment³. However, advanced or recurrent cervical cancer prognosis remains poor. Five-year survival rate of metastatic disease is approximately 16.5 % and almost 13 % of women are in this stage at the time of diagnosis³.

Development in the management of cervical cancer is not very rapid. Over the past 60 years, only a few major

advances have been achieved. Firstly, the introduction of Pap smear as a screening modality in the 1950s and it led to 60% reduction in the mortality from cervical cancers⁴. Addition of cisplatin to radiation therapy is another milestone in the development of cervical cancer and it was shown in many clinical trials and retrospective studies that the mortality risk decreases by 30-60 %⁵. Since then, no further development has been seen, until the addition of bevacizumab agent to the combination chemotherapy reported to show a 3.7 months advantage in overall survival rate in 2014⁶.

Various studies are on-going on in which the main focus is on the therapies that selectively target the specific molecular pathways involved in tumorigenesis and which may result in the major advancement in the management of cervical carcinoma. Here we briefly discuss current and developing therapies in locally advanced, recurrent, and metastatic cervical cancer and their specific role in clinical practice.

Standard Chemotherapy

It has been shown that the introduction of

chemotherapy with radiotherapy is associated with significant improvements in the overall survival rates. Until recently, chemotherapy use was limited to patients with metastatic or recurrent cancer only.

In patients with limited metastatic diseases (like solitary lung metastasis, central pelvic recurrence or disease in para-aortic nodes), long-term survival can be increased with the surgical resection and or radiation therapy⁷⁻¹⁰.

Many chemotherapeutic agents like microtubular inhibitors, anthracyclins, anti-metabolites and alkylating agents have been shown in many studies to have activity in previously untreated patients as a single agent¹¹. Cisplatin has been considered the most active drug and current trials suggest that platinum-based combination may be more effective. The combination therapy of cisplatin and paclitaxel had a higher response rate (RR) and improved period free survival compared with single-agent therapy with cisplatin, but there was no improvement in the overall survival rate¹². The combination therapy of cisplatin and topotecan compared with single-agent therapy with cisplatin showed an improvement in overall response rate, progression free-survival (PFS), and overall survival (OS)¹³. However, the toxicities and side effects were significant with this combination and 70% of patients had grade 3 or 4 neutropenia (compared with 1.4% in cisplatin single agent therapy).

The efficacy of four platinum-based drugs was studied in a large randomized trial¹⁴. Patients were randomly given cisplatin in combination with either paclitaxel, vinorelbine, gemcitabine, or topotecan. This study showed that paclitaxel is superior to other three drugs in terms of OS and trend in response rate, PFS and OS favored paclitaxel.

Moore et al, did a study to find out the high-risk factors which are independently related to the poor response to the cisplatin chemotherapy, and thus help in selecting the patients who would be least benefited from this therapy. These include APS (average performance status) > 0, pelvic disease, prior radio-sensitizing cisplatin, and PFS < 1 year. The response rate is only 13 % if the patients had 4 to 5 risk factors and thus not a good candidate for cisplatin-based chemotherapy. These patients should be considered for non-cisplatin-based chemotherapy or investigational trials¹⁵.

Combination chemotherapy of carboplatin and paclitaxel is reported as being a more rational option because of more favorable toxicity profile, than the combination of cisplatin and paclitaxel. In one randomized trial it was shown that there was no significant difference in overall survival between two

combinations but less hospitalization was seen with carboplatin and paclitaxel combination¹⁶. Thus, this is a more preferred combination therapy.

Other treatment options are limited and they include ifosfamide, paclitaxel, topotecan, irinotecan, capecitabine, pemetrexed, vinorelbine, and nabpaclitaxel are among the most active single agents, while docetaxel, gemcitabine, and ixabepilone were found to have minimal activity¹⁷⁻²³.

Sentinel lymph node biopsy (SNLB)

It is a technique where instead of removing many lymph nodes, only few lymph nodes are targeted which are most likely to contain tumor deposits. In this technique, a radioactive agent (blue dye) is injected into cancer and the dye allowed to drain by the lymph nodes. During the surgery, only the lymph nodes containing radiation and blue dye are removed. If these particular lymph nodes don't contain cancer cells then there is no need to remove other lymph nodes and this will reduce the incidence of postoperative complications like lymphedema of legs.

Many clinical trials have been done showing the mapping of lymph nodes by using laparoscopic-assisted infrared imaging after the injection of dye indocyanine green into the cervix. Current studies showed that the sentinel lymph node biopsy is very helpful for the early stages of cervical cancer but more clinical trials are required to see that whether this procedure should routinely become a part of the standard treatment or not.

Immunotherapy

In patients suffering from cancer, the immunological system of the body is not able to control the rapid growth of cancer cells. Recently, certain new drugs have been developed that act as inhibitors of immune check-points and lead to the resetting of the immune system. These drugs boost the natural defense mechanism of the body and they are developed from material made either by the body or in the laboratories to improve or restore the immune system. These drugs have been found to be very efficient in the treatment of different types of cancer. Many trials are undergoing to know the efficacy of immunotherapy in cervical cancer treatment. Therapeutic vaccines are developed which are used in the patients who have already had cervical cancer and these vaccines boost the immune system to recognize cancer cells and destroy them.

Immunotherapy for cancers has had enormous advances in the recent years. Suppression of the immune system is the major risk factor for the cervical cancers and its increased rates have been seen in conditions like

autoimmune diseases, use of immune-suppressants, end stage renal disease, organ transplantation, AIDS or history of smoking²⁴.

Adoptive T-Cell Therapy

It is a therapy where autologous T cells were identified which aim for the specific targets and these cells are cultured through ex-vivo culture media. These cultured cells are then infused in the patients as tumor infiltrating lymphocytes which identify and destroy the target tumor cells in advanced malignancies²⁵. Autologous T cells have been shown to have a complete response in B-cell hematological malignancies and melanoma but had limited data in cases of epithelial malignancies²⁶.

A large randomized trial was conducted in 2015 in which HPV targeted ATC therapy was studied in metastatic cervical cancers. Out of nine patients who received ATC therapy, one achieved partial and 2 achieved the complete response. These two complete responses were still ongoing after treatment²⁷.

Targeted therapy

Certain new drugs have been developed that specifically target the gene changes in cells that cause cancer. Targeted therapy also targets proteins and particular tissue environment that promotes cancer cell growth and survival. These drugs work differently from the standard chemotherapeutic agents and have less severe side effects. They can be used alone or in combination with the standard chemotherapy drugs.

Angiogenesis inhibitors that inhibit the action of protein named vascular endothelial growth factor (VEGF) have been shown to be helpful in women with metastatic cervical cancer and increase their life-span. This has been the most efficacious adjunct to the treatment of advanced cervical cancer. The goal of these drugs is to starve the tumor cells by inhibiting the supply of nutrients. The combination of bevacizumab (an angiogenesis inhibitor) and chemotherapy were highly effective in advanced cervical cancer^{28,29}.

Pazopanib is one type of targeted drug that inhibits certain growth factors that help cancer cells to grow rapidly. Certain studies showed that this drug is effective in advanced cervical cancer and further studies are continued.

Many other anti-angiogenics, principally in the form of VEGF or VEGF-R tyrosine kinase inhibitors, have been studied with varied results. Sunitinib, pazopanib, and brivanib have had minimal activity³⁰⁻³².

Other Targets

Multiple trials have been going on to evaluate the

efficacy of targeted agents. However other agents like EGFR inhibitors (erlotinib, lapatinib, cetuximab) or mTOR inhibitor (temsirolimus) were found to have less activity³³⁻³⁵.

Other targets include HER2, WEE1, Notch signaling, heat shock protein 90, and other PARP inhibitors. However, many of these studies are at their early stages, either in the preclinical phase or unpublished pilot clinical studies³⁵.

Therapeutic Vaccines

Another advancement in the management of recurrent or advanced cancer cervix is a vaccine (ADXS11-01 (axali- mogene filolisbac), consist of live attenuated *Listeria monocytogenes* bioengineered to produce an HPV16-E7 fusion protein, which, when identified by antigen-presenting cells, activates the T helper cell immunity and produces cytotoxic T cells that target HPV-E7-transformed cells in the tumor, while simultaneously suppressing the immunologic tolerance within the lesions. Phase 2 study over 110 patients of ADXS11-001 for the treatment of persistent or recurrent cervical cancer in Indian women, showed that the 12-month overall survival was 36%, the response rate was 11%, and disease control rate was 43%. Previous therapy, baseline performance status, and the combination with cisplatin had no effect on survival or response³⁶. The FDA has already approved the initiation of a phase III trial (NCT02853604).

Similarly, the Peptide vaccines initiate immunity through the injection of a peptide epitope into the patient, leading to the same aforementioned mechanism of T-cell mediated immunity against the tumor. Recently, a phase 2 study was conducted of a peptide cocktail vaccine (which includes the VEGF receptor peptide) in advanced and metastatic cervical and ovarian cancer, showing that out of the 21 cervical cancer patients, 2 complete responses were observed, with a median overall survival of 15.4 months³⁷. There were no major side effects, proved that peptide vaccines can be safe and effective option in cervical cancer.

Though many other trials have studied the effect of different therapeutic vaccines in both early and advanced cervical cancer, many have reported non interpretable results or minimal activity, while others are new and in preclinical stages³⁸.

Monoclonal Antibodies: Inhibiting Inhibitors

Inhibitors of programmed cell death protein 1 and cytotoxic T-lymphocyte associated antigen-4 (CTLA-4) are recently studied based on the fact that the immune checkpoint inhibitors have marked clinical efficacy and

suppression of immune system plays an important role in cervical cancers. This inhibition of proteins boosts the immunological system to fight against the cancer cells and also affects the defense mechanism of cancer cells by inhibiting the proliferation and cytokine secretion.

Many monoclonal antibodies are currently in clinical trials with highly promising results, including nivolumab (NCT02257528, NCT02488759), ipilimumab (NCT01711515, NCT01693783), and durvalumab/tremelimumab (NCT01975831).

Hyperthermia

Some studies showed that the addition of hyperthermia to radiation therapy may help to keep cancer from coming back and help patients live longer. In this treatment, the temperature is increased in the area where the cancer is present, most frequently by using radiofrequency probes placed around the patients.

Fertility-preserving surgery

Many studies continue to focus on improving surgical techniques and identifying patients with cervical cancer who can be treated successfully without losing their ability to have children.

Combination therapy

Some trials are studying different combinations of immunotherapy, radiation therapy, and chemotherapy.

Palliative care

Clinical trials are ongoing to identify better ways of decreasing symptoms and side effects of current cervical cancer treatments to improve patients' comfort and quality of life.

References

1. McGraw LS, Ferrante JM. Update on prevention and screening of cervical cancer. *World J Clin Oncol.* 2014 Oct 10; 5(4): 744–52.
2. Fuentes A, Agustin A G. Advancements in Cervical Cancer Prevention and Management of Persistent, Recurrent, and Metastatic Disease: 2016 Update. *AJHO.* 2016;12(12):8-17
3. Howlander N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2012, National Cancer Institute, Bethesda, MD. Available at www.seer.cancer.gov. Accessed September 22, 2016.
4. Reis LAG, Melbert D, Krapcho M, et al. SEER Cancer Statistics Review. http://seer.cancer.gov/csr/1975_2004/results_merged/sect_05_cervix_uteri.pdf. Accessed September 22, 2016.
5. Hsu HC, Li X, Curtin JP, Goldberg JD et al. Surveillance epidemiology and end results analysis demonstrates improvement in overall survival for cervical cancer patients treated in the era of concurrent chemoradiotherapy. *Front Oncol.* 2015;5:81.

6. Tewari KS, Sill MW, Long HJ, et al. Improved survival with bevacizumab in advanced cervical cancer. *N Engl J Med.* 2014; 370(8): 734-43.
7. Lim MC, Lee HS, Seo SS, et al. Pathologic diagnosis and resection of suspicious thoracic metastases in patients with cervical cancer through thoracotomy or video-assisted thoracic surgery. *Gynecol Oncol.* 2010;116(3):478-82.
8. Tran PT, Su Z, Hara W et al. Long-term survivors using intraoperative radiotherapy for recurrent gynecologic malignancies. *Int J Radiat Oncol Biol Phys.* 2007;69(2):504-11.
9. Marnitz S, Dowdy S, Lanowska M et al. Exenterations 60 years after first description: results of a survey among US and German Gynecologic Oncology Centers. *Int J Gynecol Cancer.* 2009; 19(5): 974-7.
10. Long III HJ. Management of metastatic cervical cancer: review of the literature. *J Clin Oncol.* 2007;25(20):2966-74.
11. Vermorken JB. The role of chemotherapy in squamous cell carcinoma of the uterine cervix: a review. *Int J Gynecol Cancer.* 1993; 3(3):129-42.
12. Moore DH, Blessing JA, McQuellon RP et al. Phase III study of cisplatin with or without paclitaxel in stage IVB, recurrent, or persistent squamous cell carcinoma of the cervix: a GOG study. *J Clin Oncol.* 2004;22(15):3113-9.
13. Long HJ, Bundy BN, Grendys EC (Gynecologic Oncology Group Study). Randomized phase III trial of cisplatin with or without topotecan in carcinoma of the uterine cervix: a GOG Study. *J Clin Oncol.* 2005;23(21):4626- 33.
14. Monk BJ, Sill MW, McMeekin DS, et al. Phase III trial of four cisplatin-containing doublet combinations in stage IVB, recurrent, or persistent cervical carcinoma: a GOG study. *J Clin Oncol.* 2009; 27(28):4649-55.
15. Moore DH, Tian C, Monk BJ et al.. Prognostic factors for response to cisplatin-based chemotherapy in advanced cervical carcinoma: a GOG Study. *Gynecol Oncol.* 2010;116(1):44-9.
16. Kitagawa R, Katsumata N, Shibata T et al. Paclitaxel plus carboplatin versus paclitaxel plus cisplatin in metastatic or recurrent cervical cancer: the open-label randomized phase III trial JCOG0505. *J Clin Oncol.* 2015; 33(19):2129-35.
17. Muderspach LI, Blessing JA, Levenback et al. A phase II study of topotecan in patients with squamous cell carcinoma of the cervix: a GOG study. *Gynecol Oncol.* 2001;81(2):213-5.
18. Garcia AA, Blessing JA, Darcy KM et al. Phase II clinical trial of capecitabine in the treatment of advanced, persistent or recurrent squamous cell carcinoma of the cervix with translational research: a GOG study. *Gynecol Oncol.* 2007;104(3):572-9.
19. Look KY, Blessing JA, Michener CM et al. Phase II evaluation of capecitabine in refractory nonsquamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. *Int J Gynecol Cancer.* 2008;18(4):773-8.
20. Lorvidhaya V, Chitapanarux I, Phromratanapongse P et al. Phase II study of capecitabine (Ro 09-1978) in patients who have failed first line treatment for locally advanced and/or metastatic cervical cancer. *Gan To Kagaku Ryoho.* 2010;37(7):1271-5.
21. Burotto M, Edgerly M, Poruchynsky M et al. Phase II clinical trial of ixabepilone in metastatic cervical carcinoma. *Oncologist.* 2015; 20(7):725-6.
22. Alberts DS, Blessing JA, Landrum LM et al. Phase II trial of nab-paclitaxel in the treatment of recurrent or persistent advanced cervix cancer: A GOG study. *Gynecol Oncol.* 2012;127(3):451-5.
23. Lorusso D, Ferrandina G, Pignata S et al. Evaluation of pemetrexed (Alimta, LY231514) as second-line chemotherapy in persistent or

- recurrent carcinoma of the cervix: the CERVIX 1 study of the MITO (Multicentre Italian Trials in Ovarian Cancer and Gynecologic Malignancies) Group. *Ann Oncol*. 2010;21(1):61-6.
24. Dugue PA, Rebolj M, Garred P et al. Immunosuppression and risk of cervical cancer. *Expert Rev Anticancer Ther*. 2013;13(1):29-42.
 25. Tinker AV, Ellard S, Welch S et al. Phase II study of temsirolimus (CCI-779) in women with recurrent, unresectable, locally advanced or metastatic carcinoma of the cervix. A trial of the NCIC Clinical Trials Group (NCIC CTG IND 199). *Gynecol Oncol*. 2013; 130(2):269-74.
 26. Hinrichs CS, Rosenberg SA. Exploiting the curative potential of adoptive T-cell therapy for cancer. *Immunol Rev*. 2014; 257(1): 56-71.
 27. Stevanovic S, Draper LM, Langhan MM et al. Complete regression of metastatic cervical cancer after treatment with human papillomavirus-targeted tumor infiltrating Tcells. *J Clin Oncol*. 2015; 33(14):1543-50.
 28. Wright JD, Viviano D, Powell MA et al. Bevacizumab combination therapy in heavily pretreated, recurrent cervical cancer. *Gynecol Oncol*. 2006; 103(2): 489-93.
 29. Takano M, Kikuchi Y, Kita T et al. Complete remission of metastatic and relapsed uterine cervical cancers using weekly administration of bevacizumab and paclitaxel/carboplatin. *Onkologie*. 2009;32(10):595-7.
 30. Mackay HJ, Tinker A, Winquist E et al. A phase II study of sunitinib in patients with locally advanced or metastatic cervical carcinoma: NCIC CTG Trial. *Gynecol Oncol*. 2010;116(2):163-7.
 31. Monk BJ, Mas Lopez L, Zarba JJ et al. Phase II, open-label study of pazopanib or lapatinib monotherapy compared with pazopanib plus lapatinib combination therapy in patients with advanced and recurrent cervical cancer. *J Clin Oncol*. 2010; 28 (22):3562-9.
 32. Chan JK, Deng W, Higgins R et al. A phase II evaluation of brivanib in the treatment of persistent or recurrent carcinoma of the cervix: An NRG Oncology/Gynecology Oncology Group study. *J Clin Oncol*. 2015 (suppl; abstr e16599).
 33. Schilder RJ, Sill MW, Lee YC et al. A phase II trial of erlotinib in recurrent squamous cell carcinoma of the cervix: a GOG Study. *Int J Gynecol Cancer*. 2009;19(5):929-3.
 34. Santin AD, Sill MW, McMeekin DS et al. Phase II trial of cetuximab in the treatment of persistent or recurrent squamous or non-squamous cell carcinoma of the cervix: a GOG study. *Gynecol Oncol*. 2011;122(3): 495-500.
 35. Eskander RN, Tewari KS. Beyond angiogenesis blockade: targeted therapy for advanced cervical cancer. *J Gynecol Oncol*. 2014; 25(3): 249-59.
 36. Petit RG, Mehta A, Jain M et al. ADXS11-001 immuno-therapy targeting HPV-E7: final results from a phase 2 study in Indian women with recurrent cervical cancer. *J Immunother Cancer*. 2014; 2 (Suppl 3): P92.
 37. Satoshi T, Shoji T, Kagabu M et al. Phase 2 studies of multiple peptides cocktail vaccine for treatment-resistant cervical and ovarian cancer. *J Clin Oncol* 33, 2015 (suppl; abstr 5567).
- Vici P, Pizzuti L, Mariani L et al. Targeting immune response with therapeutic vaccines in premalignant lesions and cervical cancer: hope or reality from clinical studies. *Expert Rev Vaccines*. 2016;15(10):1327-36

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International Image Concordance Study to Compare a Point-of-Care Tampon Colposcope With a Standard-of-Care Colposcope.

Mueller JL, Asma E, Lam CT et al.

OBJECTIVE: Barriers to cervical cancer screening in low-resource settings include lack of accessible, high-quality services, high cost, and the need for multiple visits. To address these challenges, we developed a low-cost, intravaginal, optical cervical imaging device, the point-of-care tampon (POCkeT) colposcope and evaluated whether its performance is comparable with a standard-of-care colposcope.

MATERIALS AND METHODS: There were 2 protocols, which included 44 and 18 patients. For the first protocol, white-light cervical images were collected in vivo, blinded by device, and sent electronically to 8 physicians from high-, middle-, and low-income countries. For the second protocol, green-light images were also collected and sent electronically to the highest performing physician from the first protocol

who has experience in both a high- and low-income country. For each image, physicians completed a survey assessing cervix characteristics and severity of precancerous lesions. Corresponding pathology was obtained for all image pairs.

RESULTS: For the first protocol, average percent agreement between devices was 70% across all physicians. The POCkeT and standard-of-care colposcope images had 37% and 51% agreement with pathology for high-grade squamous intraepithelial lesions (HSILs), respectively. Investigation of HSIL POCkeT images revealed decreased visibility of vascularization and lack of contrast in lesion margins. After changes were made for the second protocol, the 2 devices achieved similar agreement to pathology for HSIL lesions (55%).

CONCLUSIONS: Based on the exploratory study, physician interpretation of cervix images acquired using a portable, low-cost POCkeT colposcope was comparable to a standard-of-care colposcope.

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Management algorithms for cervical cancer screening and precancer treatment for resource-limited settings.

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Management algorithms for screen-positive women in cervical cancer prevention programs have undergone substantial changes in recent years. The WHO strongly recommends human papillomavirus (HPV) testing for primary screening, if affordable, or if not, then visual inspection with acetic acid (VIA), and promotes treatment directly following screening through the screen-and-treat approach (one or two clinic visits). While VIA-positive women can be offered immediate ablative treatment based on certain eligibility criteria, HPV-positive women need to undergo subsequent VIA to determine their eligibility. Simpler ablative methods of treatment such as cryotherapy and thermal coagulation have been demonstrated to be effective and to have excellent safety profiles, and these have become integral parts of new management algorithms. The challenges faced by low-resource countries are many and include, from the management perspective, identifying an affordable point-of-care HPV detection test, minimizing over-treatment, and installing an effective information system to ensure high compliance to treatment and follow-up.

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Optimizing secondary prevention of cervical cancer: Recent advances and future challenges.

Ogilvie G, Nakisige C, Huh WK, Mehrotra R, Franco EL, Jeronimo J.

Although human papillomavirus (HPV) vaccines offer enormous promise for the ultimate control and possible elimination of cervical cancer, barriers to uptake and coverage of the vaccine both in high- and low/middle-income settings mean that advances in secondary prevention continue to be essential to prevent unnecessary deaths and suffering from cervical cancer for decades to come. While cytology (the Pap smear) has reduced cervical cancer incidence and prevalence in jurisdictions where it has been systematically implemented in population-based programs-mainly in high-income settings-limitations inherent to this method, and to program delivery, leave many women still vulnerable to cervical cancer. Recent evidence has confirmed that screening based on HPV testing prevents more invasive cervical cancer and precancerous lesions, and offers innovative options such as self-collection of specimens to improve screening uptake broadly. In this paper, we review key advances, future opportunities, and ongoing challenges for secondary prevention of cervical cancer using HPV-based testing.

Guidelines for Authors

All members of ISCCP are requested to send manuscripts pertaining to (but not exclusively limited to) to cervical cancer prevention/treatment for publication in the newsletter. The matter should be original and not published/under consideration for publication elsewhere. This could be in one of following forms:

1. **Original Article:** Articles from original research (including aim, methods, results and discussion), should not exceed 5-6 typed pages, word limit of 1500 words and not more than 10 references. Tables and Figures could be included as per requirement.
2. **Review Article:** The article should not exceed 3-4 typed pages, word limit 1200 words with not more than 8 references.
3. **Case Report:** An interesting case report which has "take home message", word limit 800 words with not more than 3-5 references.
4. **Report of awareness/training camps:** up to 300 words with 2-3 images

References: References should be recent, relevant, indexed and in Vancouver style. References to literature cited should be numbered consecutively and placed at the end of the manuscript. In the text they should be indicated as superscript.

All papers submitted are subject to review process. All accepted papers will be suitably edited before publication.

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ISCCP Activities

Colposcopy Courses by RCOG

AICC-RCOG-NZ India organized **Biannual Colposcopy Course-Basic & Advanced** under Aegis of ISCCP, approved by the International Federation of Colposcopy & Cervical Pathology on 18th & 19th June 2017. The course material included didactic lectures, picture quiz,



case discussions on management options & follow-up, hands-on module to refresh hands-on training in colposcopy & LEEP. Around 50 delegates benefited from interaction with eminent faculty from Delhi, Trivandrum, Ahmedabad, Pune and Mumbai. The delegates from India, Bangladesh, Dubai, Abu Dhabi and Nepal participated enthusiastically enjoyed interacting with teachers with positive feedback.

Cervical Cancer Awareness Drive

The first phase of “Cervical Cancer Awareness, Screening and Vaccination Drive” as a part of community reach out project organised by Okti Foundation, Sant Parmanand Hospital, Sitaram Bhartia Institute



in association with ONGC and supported by FOGSI, AOGIN INDIA, AOGD, IMS, RCOG NZ India, ISCCP, Friends Of SPH, Inner Wheel, Rotary and She Cares Foundation was conducted on 5th October 2017. The purpose was to reach out to women and young girls belonging to low socioeconomic status and impart them education regarding the prevalence of cervical cancer in India, its risk factors, symptoms and spread awareness regarding importance of screening for and vaccination against it. The awareness phase comprised of health talks and registration for screening/vaccination was organised at Shiv Mandir, JJ Bandhu camp Vasant Kunj. Nearly 140 women registered for screening and 40 girls for vaccination in the second phase. In the end, food was distributed to the participants and their families.

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