Volume 4 | Issue 1 | January - April 2013 | Price Rs. 5.00

E-Newsletter

ISCCP
Member International Federation of Colposcopy

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

www.isccp.co.in

From the Editorial Board

Dear Friends,

As we start another year of academic activities under ISCCP, we look back to reflect on the year gone by. Highlights of last year included the addition of new members to our fraternity and many conferences/workshops were organized throughout the country under the aegis of ISCCP. Camps were conducted in remote areas to screen women & spread the message of cervical cancer prevention.

We are presently in a part of India where women fortunately are on an equal platform with men; well aware about ante-natal care; however their awareness regarding cervical cancer screening in scant & willingness amongst carers lacking.

We are personal & family doctors for our women; let us care for them not just during childbirth but all through their life! A cervical cancer screen is as important to them as a haemoglobin in pregnancy.

"Change your thoughts and you can change your world" .....Norman Vincent Peale

Best Wishes
Ed & Co-Ed'

Announcement

All life members of ISCCP are requested to pay Rs 1,250/-to retain their membership of International Federation of Colposcopy for 5 years. Cheques in favor ISCCP may be sent to:
President ISCCP
60 A, Pocket B, Mayur Vihar Phase II, Delhi 110 091, India.

Forthcoming Events

9th Annual Conference of ISCCP
March 2014 at Kolkata
organizing secretary:
Dr Rahul Roy Chowdhary

Contents

Novel Approaches in Cancer Cervix - Prevention and Diagnosis

Dr Indira Prasad
Senior Resident, Department of Obst. & Gynae., Lady Hardinge Medical College and Smt Sucheta Kriplani Hospital, New Delhi

Introduction

Worldwide, cervical carcinoma continues to be a serious health care problem and is the second most frequent cause of cancer death in women.[1] The incidence of cervical cancer varies with age. It is the most common cancer diagnosed in women younger than 35 years. Novel approaches in prevention and diagnosis will go a long way in reducing the morbidity and mortality from cervical cancer.

Novel Approaches in Vaccination

Persistent viral infection with oncogenic types of HPV is known to lead to 100% of cervical cancers (HPV 16 & 18 accounting for 70%), 90% of anal cancers, 40% of vulvar and vaginal cancers, 12% of oropharyngeal cancers and 3% of oral cancers. Fortunately, the anti-HPV vaccines (Cervarix-Recombinant HPV Bivalent Vaccine and Gardasil-Recombinant HPV Quadrivalent Vaccine) have shown to reduce the combined incidence of persistent infection or disease due to HPV 6,11,16, or 18 by 90% (P, 0.0001).[2,3,4]

Novel Approaches in Screening

Screening techniques for cervical cancer have included conventional exfoliative cervicovaginal cytology i.e. the cervical (Pap) smear, automated thin layer preparation (liquid based cytology), automated cervical screening techniques, Neuromedical systems, HPV testing, Polar probe, Laser induced fluorescence, visual inspection of cervix after applying Lugol's iodine (VILI) or acetic acid (VIA), speculoscopy and cervicography.

Currently, Pap smear is regarded as the gold standard for cervical cancer screening. Abnormal Pap smear report is an indication for colposcopy. In the previous strategies of screening, HPV DNA testing was kept optional and did not play much role in guiding the physician.

In the recent scenario, the NHS Cervical Screening Programme (NHSCSP)[5] guidelines have provided a novel approach towards cervical cancer screening by regularly including HPV DNA testing. Women are invited for regular cervical screening every 3 years (between 25 and 49 years) or every 5 years (between 50 and 64 years). Most screening is conducted using liquid-based cytology. Cytological assessment is performed to detect nuclear abnormalities, which are described as dyskaryosis. The degree of dyskaryosis can range from mild to severe, or borderline changes may be seen. The next step depends on cytology results and the presence or absence of high-risk HPV. According to their guidelines, women with borderline changes or mild dyskaryosis on cytology who are also HPV positive should be referred for colposcopy, while those who are HPV negative are returned to routine recall (3 yearly). This is referred to as HPV Triage. Women who have 3 consecutive inadequate samples or who have a test result showing moderate or severe dyskaryosis, possible invasion or possible glandular neoplasia, should be referred for colposcopy in the first instance. Reduced repeat testing in women with borderline changes or mild dyskaryosis as was being done previously reduces missed appointments and saves cost also. An example is shown in Table 1.

HPV is also used as a Test of Cure by employing high-risk HPV (HR-HPV) testing of women who have been treated for any grade of CIN to assess their risk of having residual or recurrent disease. The traditional follow up of treated women in the NHSCSP has involved annual screening for up to 10 years before their return to routine recall. However, it is now known that women who have normal cytology and are negative for HR-HPV at their follow up screening appointment are at very low risk of residual disease and need not be recalled for their next screening appointment for a further three years. Women who have received treatment for CGIN or for invasive disease are excluded from the test of cure protocol.

Table 1: Patient pathway in HPV Triage and Test of Cure versus Standard treatment

HPV Triage and Test of Cure	**Standard treatment**
Routine screen	Routine screen
Borderline cytology, HPV+	Borderline cytology
Colposcopy at 8 weeks from date of test	Repeat at 6 months, borderline cytology
CIN3 detected	Repeat at 6 months, borderline cytology
Treated with LLETZ	Colposcopy 14-18 months from date of initial test
Test of cure at 6 months, negative	CIN3 detected
3 year recall	Treated with LLETZ
Time for whole episode: 9 months	Annual follow-up for 10 years
	Time for whole episode:12 years

By employing the HPV test of cure approximately 80% of treated women avoid having to undergo annual cytology tests. There is more rapid identification of high grade CIN, shorter patient journey times and rapid resolution of uncertain screening episodes by reaching a definitive endpoint.

Novel Approaches in Diagnosis

Colposcopy occupies a key role in the prevention of cervical cancer by identifying preinvasive or invasive lesions. However, the subjective nature of colposcopy means that it is prone to considerable inter- and intra-operator variation. The adjunctive colposcopy technologies 6 like DySIS (Fig 1) and Niris Imaging System (Fig 2) are novel methods for diagnosis of preinvasive and invasive lesions of cervix.

DySIS (Dysismedical Ltd, Edinburgh, UK) is a clinical and cost-effective option for examining the uterine cervix in women referred for colposcopy. It is a digital video colposcope that also uses dynamic spectral imaging to evaluate the blanching effect of acetic acid to the epithelium (acetowhitening). It produces a quantitative measurement of the rate, extent and duration of the acetowhitening. The dynamic map (DySIS map) produced can be overlaid on a colour image of the tissue to help the clinician determine the presence and grade of any lesion. DySIS consists of an optical head with a white light-emitting diode for uniform illumination, and magnification optics coupled to a camera for image capture. It also includes a computer and control electronics unit with monitor for image and data display. The optical head does not come into contact with the tissue. It magnifies images between 10 and 27 times. It is mounted on a mechanical arm to position and stabilise it, and locked onto an extension shaft attached to a special speculum, to ensure a stable field of view during image acquisition. The average duration of use per examination is less than 15 minutes.

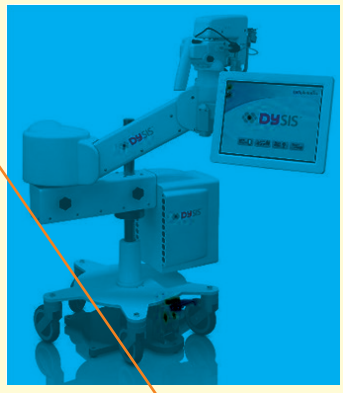

Fig. 1: Dysis Colposcope

The **Niris Imaging System** (Imalux, Cleveland, Ohio, USA) is a non-invasive device designed to aid in the detection and diagnosis of early-stage disease. It is used for guidance of biopsy and surgery, and in post-treatment surveillance. It uses near-infrared light to produce real-time, high resolution, cross-sectional imaging of tissue microstructure. The major claimed benefit of the Niris Imaging System is its ability to scan multiple layers of epithelial tissue, providing an optical biopsy up to a depth of 1.6 mm. The Niris device consists of an image-management console, laptop interface, 2.7 mm front-viewing screen and flexible optical probe that touches

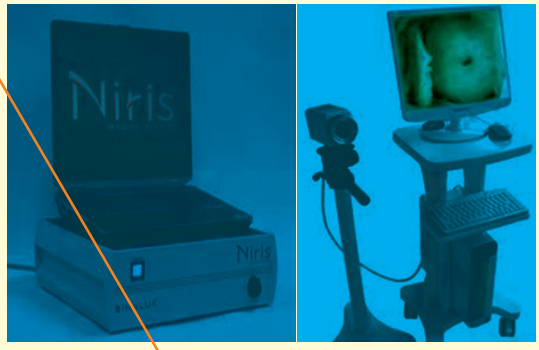

Fig. 2: Niris Imaging System and Colposcope

the tissue. The image acquisition and measurement tools are sufficiently fast (two minutes per study) to allow image data to be analysed in real time. The Niris probe can be used for around 200 procedures, and may be processed for re-use. According to the manufacturer, the average duration of use per examination (Niris imaging system and colposcopy combined) is around 4 minutes.

Use of Biological Markers in Cancer Diagnosis[7]

One of the possible approaches to early detection of cervical neoplasia is by studying protein expression of putative molecular markers. Studies have shown that the expression of proliferation markers like pKi-67, PCNA, Cyclins (A and B), over expression of CDK-inhibitors like p16, apoptotic markers like bcl2/bax ratio, p53, heat shock protein 27 and minichromosome maintenance proteins is modulated by HPV infection. This can help in detecting and distinguishing benign, precancerous and cancerous lesions.[7] This is also summarised in Table 2.

Proliferation markers (pKi- 67, PCNA)

pKi- 67 is expressed in proliferating cells and can provide a reliable means of rapidly evaluating the growth fraction of normal and neoplastic human cell populations. Proliferating cell nuclear antigen (PCNA) has also been used as a marker of cell proliferation, although its practical value is limited owing to a lower specificity for replicating cells.

Cyclins

Regulation of the cell cycle depends on the sequential activation and inactivation of cyclin dependent kinases (CDKs), through the periodic synthesis and destruction of cyclins. The levels of cyclins D1 and E are frequently increased in cancers. In cervical squamous lesions, cyclin D1 expression is blocked by high risk but not low-risk HPV infection, whilst cyclin A and cyclin E expression is unregulated by both groups of viruses. Moreover, cyclin B expression is unregulated in high-grade squamous intraepithelial lesions (CIN II, CIN III) but not in low-grade lesions (CIN I, condylomata). Recent work has revealed increased expression of cyclin A and cyclin B and to a lesser extent cyclin E, in glandular cervical neoplasia.

Cyclin-dependent kinase (CDK) inhibitors

Cyclin-dependent kinase inhibitors (CDKIs) play an important role in regulation of the cell cycle. CDKIs compete with CDKs at the binding sites with cyclins and prevent cell synthesis. Inactivation of CDKIs is implicated in the aetiology of various malignant tumours (e.g. breast, pancreatic and bladder carcinomas, etc.) Two groups of CDKI have been identified: the p21 and the p16 family of inhibitors. Strong p16 over-expression is observed in cervical squamous intra-epithelial lesions (CIN) and squamous cell carcinomas that are associated with high risk HPV types, indicating that the suppressor function of p16 can be overcome in the presence of viral oncoproteins, particularly E7. Recently, p16 has been found to be a useful diagnostic marker for neoplastic cervical squamous and glandular lesions. In addition, p16 may be useful in the distinction between cervical glandular intra-epithelial neoplasia (CGIN) and benign lesions.

Markers of apoptosis (Bcl2, p53, hsp-27)

Bcl2 extends cell survival by blocking apoptosis. Positive staining has been found in a proportion of cervical adenocarcinomas suggesting that it may have a role in the evolution of these tumours through inhibition of apoptosis.

Mutations of p53, a tumour suppressor gene, are the most frequent mutations encountered in human tumours. However, p53 mutation is uncommon in cervical neoplasia. Rather, HPV E6 protein binds to and inactivates p53 causing over-expression of wild-type p53 protein. The wild p53 protein modulates the bcl2/bax equilibrium. Loss of p53 expression and increased bcl2/bax ratio may lead to prolonged cell survival without tumour progression.

Heat shock protein (hsp) 27 is thought to protect cells from various stresses such as supra-optimal temperature, anoxia or chemical agents. The expression of hsp27 has been shown to correlate with resistance to stress. Recent data has shown that with a cut-off value of 40% for hsp27 expression neoplastic lesions may be identified from their benign mimics.

Minichromosome maintenance proteins

Minichromosome maintenance proteins (MCMs) serve as

Table 2: Summary of useful molecular markers in cervical cancer diagnosis

MOLECULAR MARKER	TO DIFFERENTE BETWEEN
CYCLIN B	TEM and CGIN
Ki 67	CIN and metaplasia and atrophy
	Cervical adenocarcinoma and benign glandular lesions
p16 $^{INK\ 4a}$	CIN and metaplasia and atrophy; CGIN and TEM
p53	Cervical adenocarcinoma and benign glandular lesions
Bcl2	TEM and CGIN
	Cervical adenocarcinoma and benign glandular lesions
CEA	Squamous and Cervical or endometrial adenocarcinoma
ChromograninA	Neuro-endocrine carcinoma and other neoplasia
Synaptophysin	Neuro-endocrine carcinoma and other neoplasia
Vimentin	Cervical and endometrial adenocarcinoma

CEA, Carcino-embryonic antigen; CIN, cervical intra-epithelial neoplasia: CGIN, Cervical glandular intra-epithelial neoplasia ; TEM, tubo-endometroid metaplasia

specific markers for proliferating cells. MCMs are ubiquitously expressed in cancer cells. Furthermore, the positive rate and level of MCM expression appeared to be higher in cancer cells than in normal proliferating cells of the uterine cervix and dysplastic cells, suggesting that they may be useful diagnostic markers.

Bibliography

1. Berek S. Jonathan. Berek and Novak's Gynaecology. 15th ed. Philadelphia: Lippincott Williams & Wilkins; 2012; Chapter 36, Cervical and Vaginal Cancer ; p1304
2. Ault A Kevin. Effect of prophylactic human papillomavirus L1 virus-like-particle vaccine on risk of cervical intraepithelial neoplasia grade 2, grade 3, and adenocarcinoma in situ: a combined analysis of four randomised clinical trials. Lancet 2007; 369: 1861-68
3. Villa LI, Costa RIA, Petta CA et al. Prophylactic quadrivalent human papillomavirus (types 6,11,16,and 18), virus-like partcle vaccine in young women: a randomized double-blind placebo-controlled multicentre phase II efficacy trial. Lancet Oncol 2005;6:271-278
4. Harper DM, Franco EI, Wheeler CM et al. Sustained efficacy upto 4.5 years of a bivalent L1 virus-like particle vaccine against human papillomavirus types 16 and 18: follow-up from a randomized control trial. Lancet 2006;367:1247-55
5. HPV Triage and Test of Cure Implementation Guide. NHS Cancer Screening Programmes; July 2011.
6. Adjunctive colposcopy technologies for examination of the uterine cervix – DySIS and the Niris Imaging System. National Institute for Health and Clinical Excellence. August 2012. NICE diagnostics guidance 4 www.nice.org.uk/dg4
7. El-Ghobashy Alaa, Herrington Simon. Cervical Cancer: epidemiology and molecular characterisation. Progress in Obstetrics & Gynaecology. 16thed. Churchill Livingstone.2006

Report of AICC RCOG Pre-conference Colposcopy Course and hands-on Workshop on 28th and 29th August 2013

Colposcopy course and hands-on workshop was organized on 28th and 29th August 2013 by the Department of Minimal and Natural Access Gynae & Gynae Cancer Surgery Fortis Vasant Kunj and Fortis memorial research institute, Gurgaon at Fortis memorial research Institute, Gurgaon . It was a pre conference event before annual conference of AICC RCOG.

It was attended by practicing Gynecologist from Delhi and out of Delhi.(3 spot registrations, 94 pre registered candidates out of which 87 reported) This workshop continued for 2 days including didactic lectures by 29 renowned faculty from all over India, interactive case discussions with experts. There was hands-on session on day second of workshop

Delegates were divided into 12 groups and learnt handling of colposcope, colposcopic and cautery instruments and settings, cervical biopsy, LEEP conization on pelvitrainers under supervision of experienced faculty.

Three new Colposcopy Trainees were inducted and successfully completed their training during this period.

Dr Anju demonstrating in Hands-on session

Auditorium full view

Dr Jha answering questions of audience

Dr Jha And Dr Indrani Ganguly Interacting with audience

Audience with Lectures in progress

Inauguration

Busy registration counter

Published from ISCCP Secretariat, Department of Obstetrics & Gynaecology, MAMC & Lok Nayak Hospital, New Delhi 110 002 on behalf of Indian Society of Colposcopy & Cervical Pathology (Reg.). **Publisher-** Dr. Vijay Zutshi, **Editor-** Dr. Saritha Samsunder, **Printed at** Process & Spot, C-112/3, Naraina Industrial Area, Phase I, New Delhi 110 028

HALL B - DAY 1				
Time	**Track**	**Topic**	**Speaker**	**Chair Persons**
08:30-09:30	Free Paper Presentation			Sushil Giri Basab Mukherjee Mousumi De (Banerjee)
09:30-09:50	Miscellaneous	Management of LSIL on histology	Sukumar Barik	Meena Nayak
09:50-10:10		Colposcopy in detection of vulvar abnormalities	Shalini Rajaram	Dibyendu Banerjee
10:10-10:30		HPV Genotype distribution in cervical neoplasias- Indian Perspective	Priya Abraham	
10:30-10:50		Lower genital tract infections other than HPV and HIV and cervical carcinogenesis	Veena Acharya	
11:00-11:30	Debate	Treatment of CIN can be done after biopsy confirmation only	Asha Jain , Bhagyalaxmi Nayek	Moderator - Abraham Peedicayle
11:30-11:50	HPV Vaccination	HPV vaccines- Principles and mechanism of action	Krishnendu Gupta	
11:50-12:10		HPV Vaccine implementation and outcome across the world	Saritha Shamsunder Kale	
12:10-01:00		HPV vaccination - myths and misconceptions- panel	Amita Maheshwari, Gauri Gandhi,Indrani Ganguly,Raksha Arora	Moderator- Sabhyata Gupta
01:00-01:30	Free Paper Presentation			
01:30-02:00		LUNCH BREAK		
02:30-03:30				
03:30-04:30				
HALL B- DAY 2				
09:00-11:00	PATHOLOGY WORKSHOP	Workshop on Histology of cervical precancer and cancer	Ravi Mehrotra,Sudipta Roy, Radhika Srinivasan	
		Grossing of cervical punch biopsy,Cone biopsy and Radical hysterectomy Specimen		
		Grossing of Lymph nodes after Radical Hysterectomy		
		Live viewing of cervical Histology Slides		
01:20-01:35				