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e-Newsletter

ISCCP

Member International Federation of Cervical Pathology and Colposopy

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www.isccp.in

From the Editor's Pen

Dear ISCCP members

Greetings from ISCCP and a Healthy life to all,

We all are going through tough times with the COVID-19 pandemic affecting more than 190 countries all over the world. During this time, when most of healthcare workers are busy in giving their services to the COVID-19 affected population, when most of the strategies are directed towards fighting this tough situation and leaving no stone unturned in reducing the transmission, the question arises of providing healing touch to other health problems. Delivering preventive, therapeutic and palliative cancer care during the severe coronavirus 2 pandemic is challenging, given the competing risks of death from cancer versus death from infection. A decision-making approach regarding immediate versus delayed cancer treatment during the COVID-19 pandemic should be carefully balanced keeping in view the rate of progression of the disease and morbidity from COVID-19. There is no "one size fits all" approach to delivering cancer care during the COVID-19 pandemic.

To deliver the screening and treatment for precancerous cervical lesions, all precautions should be taken by healthcare workers to protect themselves as well as others in the clinic. There are no clear recommendations but recently in an article published in International Journal of Gynaecology and Obstetrics on 8th April, 2020, Italian society for colposcopy and cervcovaginal pathology (SICPCV) had given few guidelines to deal with the screening procedures during the pandemic. Important highlights of the same are as below.

1. Patient evaluation in 2-4 weeks in following cases:
   a. Pap smear showing "squamous cell carcinoma," "atypical glandular cells, favor neoplastic," "endocervical adenocarcinoma in situ," or "adenocarcinoma".
   b. Histopathological evidence of suspected invasion from cervical/vaginal biopsy, or invasive disease after a cervical excision procedure, vaginal excision, or vulvar biopsy/excision; sudden onset of strongly suggestive symptoms for malignancy.
2. Digital imaging technologies can be used to share colposcopic images with reference centers, to avoid patient crowding in referral centres who are already busy with the COVID 19 patients.
3. All patients must undergo screening for COVID-19 exposure and should wear a surgical mask.
4. A high-efficiency filter smoke evacuation system is mandatory to remove surgical smoke. Electrosurgical instruments should be set at the lowest possible power and not be used for long continuous periods to reduce the amount of surgical smoke.
5. Personal protective equipment consisting of sterile fluid-repellant surgical gloves, an underlying pair of gloves, eye protection, mask, surgical cap, and gown should be used
6. Disposable transparent cover should be used to cover colposcope.

7. A protective lens must be disinfected after each use.
8. The use of a video colposcope is preferred.

Current issue also contains some more information on LACC trial by Dr Nikhil. Few histopathological images compiled by Dr Zeeba describing CIN 1, 2, and 3 have also been included. This issue also contains the details of activities held in the last 3 months along with 'Journal Scan' and 'News from around the world' sections.

I, once again, request all the ISCCP members to contribute in the Newsletter in the form of review articles/original articles/viewpoint/case reports/images.

Stay Home and Stay Healthy

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Cancer Cervix - LACC trial

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Background

The Phase III Laparoscopic Approach to Cervical Cancer (LACC) trial (ClinicalTrials.gov Identifier: NCT00614211) was published last year in the New England Journal of Medicine[1]. It was prospectively designed to compare oncological outcomes between open and minimally invasive surgery (MIS) for radical hysterectomy (RH) in women with early-stage cervical cancer. Globally, gynecologic oncologists were surprised to find that MIS for an RH showed significantly lower disease-free survival (DFS) and overall survival (OS) rates than those for open RH. In this trial, 631 women diagnosed according to the 2009 International Federation of Gynecology and Obstetrics (FIGO) stage IA1 with lymphovascular space invasion (LVSI), IA2, and 1B1 cervical cancer were equally and randomly assigned to an MIS RH group (n=319) and an open RH group (n=312). The median follow-up period was 2.5 (range, 0–6.3) years. At 3 years, the DFS (91.2% vs. 97.1%; hazard ratio [HR]=3.74, 95% confidence interval [CI]=1.63–8.58) and the OS (93.8% vs. 99.0%; HR=6.0, 95% CI=1.77–20.3) were worse in the MIS for RH group when compared to that in the open RH group.

Korea does around 80% of their radical hysterectomies for cancer cervix by minimal invasive technique, hence they felt the pinch of outcomes of LACC TRIAL the most.

Korean Society of Gynaec Oncology (KSOG) Adopted the Following Approach:

KSGO planned an on-line survey to ascertain the awareness of KSGO members regarding the LACC trial. The questionnaire consisted of 27 questions on basic knowledge of the respondents and the surgical procedures before/after the LACC trial. On March 2019, a hyperlink to the questionnaire was sent by e-mail using the KSGO office database, which contains 773 e-mail addresses of specialists in obstetrics and gynecology, including 268 gynecologic oncologists authorized by the KSGO. The numbers of respondents were respectively counted by each question because the respondents could choose not to participate in all questions. Several questions allowed multiple answers to be selected.

There were total of 114 (overall response rate: 14.7% [114/773]) responses to the survey, out of which 106 (response rate among gynecologic oncologists: 39.6% [106/268]) were gynecologic oncologists authorized by the KSGO. Among the respondents, gynecologists aged between 40–49 years (48/94, 51.5%), with experience as a specialist for 10–19 years (52/102, 51.0%), and who worked at university hospitals (104/114, 91.2%) were most frequent. Almost all surgeons routinely performed pelvis magnetic resonance imaging (112/113, 99.1%) and positron emission tomography-computed tomography (102/113, 90.3%) scans for cervical cancer patients before a surgery. Over one third of the respondents (43/111, 38.8%) performed 11–20 surgical procedures for cervical cancer annually.

Most respondents already knew the results of the LACC trial (114/111, 97.4%) and had read the original article

(101/114, 88.6%) at the time of the survey. However, two thirds (79/114, 69.3%) responded that the results of the trial were unexpected. The respondents suggested that immoderate tumor traction (76/114, 66.7%) and the use of the uterine manipulator (73/114, 64.0%) were main causes for the worse prognosis in the MIS group. Two thirds (67/114, 58.8%) of the respondents changed their practice after reading the results of the trial. Before the trial, 80.7% (92/114) of respondents had mainly performed an MIS (laparoscopic or robotic surgery) for surgical treatment of early-stage cervical cancer. However, more than two thirds chose to perform an open RH (73/114, 64.0%) and not adhere to laparoscopy (71/114, 62.3%) after the trial. There were few respondents who agreed that MIS for RH was appropriate for cervical cancer of 2018 FIGO stage IB2 (11/113, 9.7%) and IB3 (1/113, 0.9%). Seven respondents even suggested that there were no proper indications for an MIS for an RH in cervical cancer. More respondents concurred that performing an MIS for an RH in cases with clear resection margin (89/113, 78.8%) was more feasible than that for cases with an involved resection margin (65/111, 58.6%) after cervical conization. Most respondents would try to improve outcomes of MIS RH by minimizing the tumor traction (91/111, 82.0%). A colpotomy with minimal contact with the peritoneum (77/111, 69.4%) and the use of a closed bag for retrieved lymph nodes (67/111, 60.4%) were also considered. After the LACC trial, 66.4% (75/113) of the respondents shared the results with women scheduled for an RH for cervical cancer, and 65.5% (74/113) said that its omission was unethical. Two thirds responded that further studies are needed to confirm the results of the LACC trial (78/111, 68.4%) and intend to participate in them (80/114, 70.2%).

An MIS for cancer treatment has been more widely used in Korea than in other countries, and approximately half of all RH procedures in patients with cervical cancer were performed via laparoscopy in the 2010s[6]. Therefore, results of the LACC trial can be embarrassing for members of the KSGO. This survey showed the inner conflict among the respondents well. The majority of the respondents recognized the potential disadvantages of MIS for an RH due to immoderate tumor traction and the use of a uterine manipulator, and even changed their practice after the publication of the LACC trial. However, they also suggested that the MIS RH could be allowed in patients with cervical cancer classified as lower than FIGO stage IB2, and that the disadvantages of an MIS for an RH could be overcome in appropriate candidates by minimizing tumor traction and careful colpotomy. It seems difficult to ignore non-inferior survival outcomes of the MIS showed in previous retrospective studies after only 1 randomized trial [7-10]. Additionally, there is no lack of concern for the limitations including study design (22/114, 19.3%), enrolled patients (26/114, 22.8%), and participating surgeons (43/114, 37.7%) in the LACC trial. Although a similarly designed trial may be unethical due to safety issues, the selection of optimal candidates and development of proper methods for an MIS for RH should continue. The KSGO organized a task force team to write a position statement regarding MIS for RH in cervical cancer and recently completed the statement, and is presently discussing this issue with associated academic societies and gynecologists.

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Histopathological Images of Cervical Intraepithelial Neoplasia

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Cervical Intraepithelial neoplasia refers to histopathological description in which a part or full thickness of stratified squamous epithelium of cervix is replaced by cells showing varying degree of dysplasia (cells resembling cancer cells). However the basement membrane remains intact.

Cervical Intraepithelial Neoplasia 1 (CIN I): is associated with both low and high risk HPV subtypes. They also include condyloma which can be flat, exophytic or giant, flat being more common (figure 1).

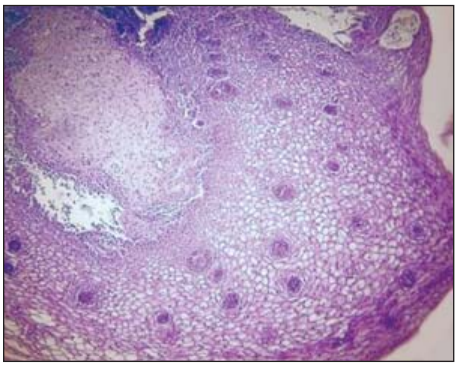

Figure 1: CONDYLOMA

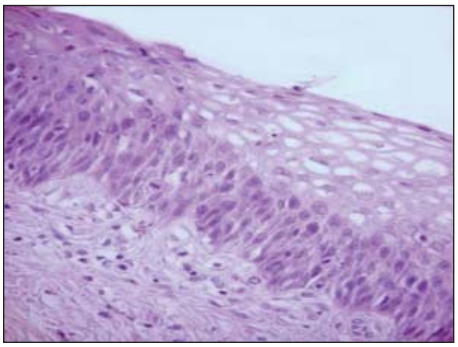

Figure 2: CIN I

Microscopically, increased thickness of the basal layer (less than one-third of the epithelial thickness) with a widespread koilocytosis (vacuolated cells) in the upper layers, together with some binucleate cells (figure 2).

Cervical Intraepithelial Neoplasia 2 (CIN II): The distinction of CIN 2 from CIN 1 is based on a number of different criteria. The nuclear atypia is more severe than CIN 1; immature proliferating cells persist up to the middle third of the epithelium where cytoplasmic maturation commences

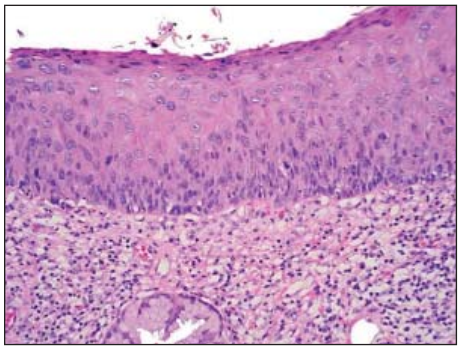

Figure 3: CIN II

Microscopic examination shows more marked basal hyperplasia (between one- and two-thirds of the epithelial thick- ness) In addition nuclei are enlarged and there are more frequent mitoses and abnormal, multipolar and fragmented mitoses indicating also a high-grade lesion (figure 3).

Cervical Intraepithelial Neoplasia 1 (CIN III): Characterized by major loss of orderly maturation of the epithelium with the deepest two-thirds or more of the epithelium replaced by immature abnormal cells with abnormal nuclei and atypical mitoses. The basement membrane remains intact in CIN III without invasion. May also be referred to as cervical carcinoma in situ.

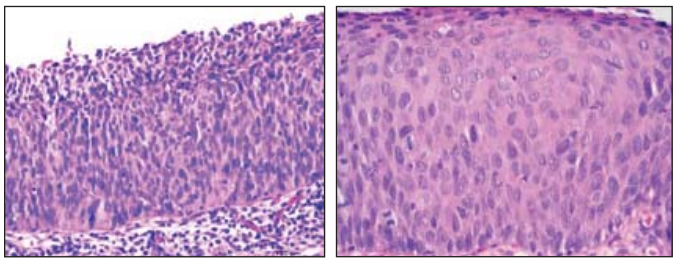

Figure 4: CIN III

Microscopically, shows abnormal cells with hyperchromatic (dark) nuclei almost filling the cells occupying almost the entire epithelium (figure 4). When the entire epithelium is replaced by uniform immature cells it is called carcinoma-in-situ, but in this example there is some flattening and differentiation of cells at the surface.

Gilham C, Sargent A, Peto J.

Triaging Women with Human Papillomavirus Infection and Normal Cytology or Low-grade Dyskaryosis: Evidence from 10-year follow up of the ARTISTIC trial cohort.

BJOG. 2020 Jan;127(1):58-68.

The triage of HPV+ women with low-grade or normal cytology is not clear.

The objective of this study was to estimate long-term CIN3 risks associated with different triage strategies for HPV positive women so as to reducing unnecessary referrals.

Methods

Women were recruited to the ARTISTIC trial after attending routine cervical screening in Greater Manchester in 2001-03 and were followed up for CIN3 and cancer notification through national registration until December 2015.

Results

The 10-year cumulative risk of CIN3+ for different groups were as follows:

- HPV16/18 infection with borderline/low-grade cytology – 19.4% (95% CI 15.8-23.8%).
- HPV16/18 infection with normal cytology- 10.7% (95% CI 8.3-13.9%)
- Other HPV types with borderline/low-grade cytology-7.3%, (95% CI 5.4-9.7%)
- Other HPV types with normal cytology- 3.2% (95% CI 2.2-4.5%)

Among the 379 women with normal to low-grade cytology and new HPV infection, the 10-year cumulative CIN3+ risk was 2.9% (95% CI 1.6-5.2%).

Conclusions

- The CIN3 risk is confined to women with persistent type-specific HPV so partial genotyping test assays identifying HPV16/18 as a minimum are essential for efficient risk stratification.
- Immediate referral to colposcopy for HPV+ women with borderline or low-grade cytology and referral after a year if still HPV+ with normal cytology may be unnecessary. Low-grade lesions can safely be retested to identify those with persistent HPV.
- Recall intervals of 1 year for HPV16/18 and 2 years for other high-risk HPVs are justified for women with normal cytology and might also be considered for women with borderline/low-grade cytology.
- The minimal risk of invasive cancer that has progressed beyond stage 1A must be weighed against the advantages of reducing the number of referrals to colposcopy.
- Thus, cervical screening would be better for women and cheaper if women with HPV and normal to low-grade cytology were retested after a year or two when many infections will have cleared.

Peeters E, Wentzensen N, Bergeron C, Arbyn M.

Meta-analysis of the Accuracy of p16 or p16/Ki-67 Immunocytochemistry versus HPV Testing for the Detection of CIN2+/CIN3+ in Triage of Women with Minor Abnormal Cytology.

Cancer Cytopathol. 2019 Mar;127(3):169-180.

Women with ASC-US cytology can be triaged accurately with a high-risk HPV test to identify those who need a referral. However, the triage of LSIL lesion with hrHPV testing has very low specificity. Overexpression of p16, with or without Ki-67, indicates neoplastic transformation of HPV-infected cervical cells and may more accurately predict underlying CIN3 or worse.

Methods

This meta-analysis selected studies that included women with ASC-US or LSIL who were triaged with dual staining (p16/Ki-67) and/or p16 staining and, if available, with a comparator hrHPV test to detect cervical intraepithelial neoplasia of grade 2 or worse (CIN2+) or CIN3+.

Results

Thirty-eight studies were eligible.

- The sensitivity of p16 staining for CIN3+ was significantly lower than that of hrHPV DNA testing:
  Ratio for ASC-US - 0.87; (95% confidence interval 0.78-0.97)
  Ratio for LSIL -0.86; (95% confidence interval, 0.80-0.93).
- The specificity of p16 staining was substantially higher than that of hrHPV DNA testing:
  Relative specificities for ASC-US - 1.60 (95% CI, 1.35-1.88)
  Relative specificities for LSIL - 2.29 (95% CI, 2.05-2.56)
- Dual staining was as sensitive as hrHPV DNA testing for LSIL
- Dual staining was more specific than hrHPV DNA testing for LSIL:
  Ratio for ASC-US- 1.65; (95% CI, 1.42-1.92)
  Ratio for LSIL- 2.45; (95% CI, 2.17-2.77).

Conclusions

This meta-analysis confirms that p16 staining and p16/Ki-67 staining are more specific for CIN2+/CIN3+ than hrHPV DNA testing. Although p16 staining is less sensitive for CIN3+ than hrHPV DNA testing, dual staining has similar sensitivity.

De Fouw M, Oosting RM, Rutgrink A, Dekkers OM, Peters AAW, Beltman JJ.

A Systematic Review and Meta-analysis of thermal Coagulation Compared with Cryotherapy to Treat Precancerous Cervical Lesions in Low- and Middle-Income Countries.

Int J Gynaecol Obstet. 2019 Oct;147(1):4-18

Thermal coagulation is gaining popularity for treating CIN in screening programs in low- and middle-income countries (LMICs) due to unavailability of cryotherapy. This review assessed the effectiveness of thermal coagulation for treatment of CIN lesions compared with cryotherapy, with a focus on LMICs.

Methods

The meta-analysis included publications with original data evaluating cryotherapy or thermal coagulation with proportion of cure as outcome, assessed by colposcopy, biopsy, cytology, and/or visual inspection with acetic acid (VIA), and minimum 6 months follow-up.

Results

Pooled cure proportions for two methods were as follows:

- *CIN 1*
  Pooled cure proportions for cryotherapy -93.8% (95% CI, 88.5-97.7)
  Pooled cure proportions for thermal coagulation - 91.4% (95% CI, 84.9-96.4)
- *CIN 2-3*
  Pooled cure proportions for cryotherapy -82.6% (95% CI, 77.4-87.3)
  Pooled cure proportions for thermal coagulation - 91.6% (95% CI, 88.2-94.5)
- *VIA-positive lesions*
  Pooled cure proportions for cryotherapy – 92.8% (95% CI, 85.6-97.7)
  Pooled cure proportions for thermal coagulation- 90.1% (95% CI, 87.0-92.8)
- Findings suggested a difference between the treatment effectiveness for CIN 2–3 lesions in favor of thermal coagulation. However, when comparing the effectiveness of both treatment modalities in LMICs only, the proportion of cure was similar: 82.6% for cryotherapy and 82.4% for thermal coagulation.

Conclusion

Both cryotherapy and thermal coagulation are effective treatment modalities for CIN lesions in LMICs.

Cervical Cancer News from Around the World

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International Women's Day: FOGSI conducts nationwide breast and cervical cancer screening for women cops

Times now News: 8 March 2020

On the occasion of International Women's Day, observed on 8th of March every year, the Federation of Obstetric and Gynaecological Societies of India (FOGSI) conducted nationwide breast and cervical cancer screening for women police personnel aged between 30 and 65 years. To raise awareness about detection, prevention and management of the conditions, more than one lakh female police personnel, including traffic police, Railway police, and CRPF families, across India were screened.

To read more: https://www.timesnownews.com/health/article/international-womens-day-fogsi-conducts-nationwide-breast-and-cervical-cancer-screening-for-women-cops-and-crpf/562374

FDA Approves Cytology Test to Improve Prevention of Cervical Cancer

March 11, 2020

The FDA has approved the CINtec® PLUS Cytology test as the first biomarker-based triage test for women whose primary cervical cancer screening results are positive for the human papillomavirus (HPV) using the cobas® 4800 HPV Test, according to Roche (Genentech), the manufacturer of the test. https://www.oncnursingnews.com/web-exclusives/fda-approves-cytology-test-to-improve-prevention-of-cervical-cancer

HPV Awareness to Eliminate Cervical Cancer

March 3, 2020

To mark the occasion of International Human Papilloma virus (HPV) Awareness Day, Cancer Council NSW's Director of Research, Karen Canfell, reminds everyone to do their part in eliminating this deadly disease.

Many women and men have HPV but what does this have to do with cervical cancer?

'In fact, recent Cancer Council NSW research has found that Australia is on track to be the first country in the world to eliminate cervical cancer, by as early as 2035.'

To read more: https://www.echo.net.au/2020/03/hpv-awareness-to-eliminate-cervical-cancer/

Returnee Invents AI Robot to Help Diagnose Cervical Cancer

March 2, 2020

The development of AI (artificial intelligence) has helped improve medical treatments. In fact, a research team, led by Sun Xiaorong, Chairperson of Wuhan Landing Medical High-tech Co., Ltd., has established the automated, intelligent and standardized Landing cyto-scanning mechanism, to provide diagnoses of cervical cancer. By applying cutting-edge AI and cloud technologies, Sun's team has helped reduce the global mortality rate (from the cancer) of women.

To read more: http://www.womenofchina.cn/womenofchina/html1/In-depth/exclusives/2003/2785-1.htm

ISCCP Activities

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Rajasthan Branch of ISCCP organised a Cervical and breast cancer prevention program in Jaipur on 4th February: All the eminent speakers from different parts of the world came to Jaipur in the 2nd World Congress on Cancer (WCC-2020) at MGM Hospital, Jaipur, where they discussed the recent updates on cancer prevention and the researches going on various cancers specially the gynaecological cancer. Prof. V. Sridevi from Cancer Institute, India spoke on "Hereditary breast and ovarian cancers: Indian scenario". Cancer Vaccine, Chemotherapy & Immunotherapy was spoken by Prof. Elizabeth M. Jaff.

Department of Obstetrics and Gynaecology, Safdarjung Hospital, under the Aegis of FOGSI and ISCCP, organized a **training of trainers(TOT) workshop on 29th February** 2020 on "Digital screening for cervical cancer" under the guidance of head of department Dr Rupali Dewan. Dr Vijay zutshi and Dr Saritha Shamsunder were the conveners of the workshop, along with Dr Sujata Das, Dr Archana Mishra and Dr Sheeba Marwah as co-conveners. The workshop was attended by 76 eminent gynecologists across medical colleges & corporate hospitals all over India. The workshop was presided over by President FOGSI Dr Alpesh Gandhi and Medical Superintendent of the hospital Dr Balvinder Arora. The programme was supported by ISCCP.

Nationwide screening camp on International Women's Day on 8th March, 2020 organised by FOGSI. This initiative was supported by ISCCP. Over 70,000 Women Police and CRPF across India were screened as part of Nationwide cervical and breast screening programme.

4 TOT for training master trainers were conducted by Govt of Madhya Pradesh and CHAI on 17th-18th Dec; 18th-19th January; 3rd-4th February and 28th-29th February supported by ISCCP. The second training for Master Trainers concluded in NSCB Medical College, Jabalpur on 17th-18th January, 2020. 25 Gynaecologists were trained. Dr Kavita HOD, member ISCCP conducted the theory and hands on training. Total 9 patients were screened during the hands-on training out of which one was found to be VIA positive (CIN 2). Participants independently performed VIA screening under Dr. Kavita's supervision.

The 4th training for Master Trainers concluded in Bhopal on 28th-29th February 2020. 17 gynaecologists were trained by Dr. Ruchi Pathak, member ISCCP. All participants performed VIA screening under Dr. Ruchi's supervision.

Madhya Pradesh has now 84 Master trainers with the support of ISCCP at 45 District Hospitals and 5 medical colleges in MP now. Subsequently, districts and medical colleges will now roll out training for SNs and MOs.