ISCCP, FOGSI Gynae Oncology, AOGIN India, Consensus Guidelines for Cervical Cancer Screening, HPV vaccination and Management in the COVID-19 Pandemic and beyond

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Introduction

India has one-fifth of the cervical cancer cases in the world. GLOBOCAN 2018 estimated over 96,922 new cases of cervical cancer and 60,078 cervical cancer deaths per annum around 2018 in India[1].Prior to the COVID-19 pandemic, cervical cancer screening and prevention efforts were stepped up in India by the introduction of the National Programme for Screening of Breast, Oral and Cervical Cancers by the Ministry of Health & Family Welfare, Government of India (2016) as well as professional societies which include Indian Society for Colposcopy and Cervical Pathology (ISCCP), Federation of Obstetric and Gynaecological Societies of India, Asia Oceania research organisation on Genital Infections and Neoplasia, India (AOGIN-India), Association of Gynecologic Oncologists of India (AGOI)[2,3]. In response to the COVID-19 pandemic caused by the *SARS-Cov-2* virus, health regulatory bodies adopted various preventive strategies and Centre for Disease Control, CDC, USA recommended that

healthcare systems prioritize urgent visits and delay elective care to mitigate the spread of COVID-19 in healthcare settings[4].Such measures resulted in suspension of all elective medical services and limited practice to emergency cases only for a considerable period; this also meant that cervical cancer screening came to a virtual standstill in India, just as it did in almost all countries affected by the pandemic. We need to rethink resumption of screening and management strategies for cervical cancer control. This will be dictated by local COVID-19 control striking a balance in patient care and physician safety. The pandemic has given us the opportunity of exploring telemedicine and telehealth services using social media, mobile phone-based applications (WhatsApp Telegram etc), phone calls, text messages in re-organising health care delivery, education and counselling[5,6]'Follow up consultations to patients can be provided using Telemedicine and Telehealth. Newer consensus guidelines by for cervical cancer screening have adopted risk-based approach and these need to be incorporated in due time[7]. These guidelines are primarily based on primary human papilloma virus testing (HPV) testing, although co-testing and cytology are also considered[7,8]. Briefly, when women have an estimated 5-year cervical intraepithelial neoplasia 3 or worse (CIN3+) risk of less than 0.15% based on past history and current test results, return to routine screening at 5-year intervals using HPV-based testing is recommended. Women with a risk estimate of CIN3+ of 4% or more need expedited treatment or colposcopy. Risk estimate tables are freely available on the National Institutes of Health website[9]. It must be understood that screening with a highly sensitive test like HPV can reduce screening intervals to five years in women with a negative test report and is the screening method of choice to be adopted if resources permit.

For cervical cancer management several organisations and societies have given their recommendations and these have been considered in this document[10,11]. Recent reviews define patients as high, medium and low priority and strategize treatments accordingly [12,13].

Principles of Screening and Vaccination during and after the COVID pandemic

HPV Vaccination

1. Measures should be taken to complete vaccination schedule of girls and young adults who have begun HPV vaccination and the next dose may be given in the next 12- 15 months[14]. Recent data shows that single dose HPV vaccination is effective and second dose may be delayed by 3-5 years[15].

2. HPV vaccination maybe continued as before in areas with no or sporadic cases. If there are clusters of cases and community transmission is on-going, guidelines maybe drawn from National and regional authorities to guide mobility of girls and women and healthcare workers to minimise *SARS-CoV-2* transmission. In Sikkim the school-based HPV vaccination has shifted to health facility based due to closure of schools during the pandemic and how this will affect coverage remains to be seen.

Screening

1. Telemedicine and Tele-health facilities should be utilised for virtual consultations to reach out to women needing vaccination and screening[5,6].

2. Women who are due for any kind of screening test should be advised to reschedule the visit once the pandemic settles and should be reassured that a delay of a few months will not have a significant impact[10, 12]

3. Whenever OPDs resume and opportunistic screening is possible it may be carried out using any method (Cytology/VIA/HPV test) ensuring that the facility is not over-crowded and social

distancing is maintained. Where possible, women should be encouraged to fix prior appointments for this purpose.

4. Institutions and hospitals should be encouraged to switch over to HPV testing using self-collected cervical sample as the method of screening. This should be promoted during the COVID pandemic as it curtails travel and therefore risk of transmission of *SARS-CoV2 virus*[14]. HPV sample kits are to be provided to the woman. The self- collected samples may be sent to the laboratory for testing. Test reports can be sent as a text message on mobile phones.

5. Women with symptoms such as irregular bleeding PV, post-coital bleeding, foul smelling discharge from vagina, with or without loss of weight or new onset back pain should report to a health care facility, cared for as a priority and receive appropriate testing and treatment.

6. Outreach extension screening clinics (aka "camps") should be avoided till the pandemic settles. Instead HPV self-collection of samples by the women can be done (enabled by step by step pictorial display of sample collection technique by healthcare workers), taking due precautions, and samples can be brought to the facility for the testing. HPV sampling kits may be distributed and collected by health care workers. Suitable logistics need to be worked out for this purpose.

Management of screen positive women

Colposcopic evaluation is determined by the screening test results. Women with low grade cytology can be triaged with colposcopy. Women with high grade smears should be scheduled as soon as possible for colposcopy and those suspicious for malignancy should definitely be seen within two weeks (Table 1). Management of an HPV positive report is given in Table 1.

Table 1: Management of abnormal reports (modified)[13,16]

	Pap report or HPV testing as primary screening test	**Management**
1.	Low-grade cervical cancer screening tests (Repeated Inflammatory, ASCUS, LSIL) • HPV Negative • HPV Positive	Colposcopy Repeat Pap in after 12 months Colposcopy in 3 months

2	High-grade cervical cancer screening tests:HSIL, ASC-H (atypical squamous cells – high grade) AGC -NOS (Atypical glandular cells, not otherwise specified)	Colposcopy/biopsy to be performed as soon as feasible.
3	Suspicious of malignancy -AGC-FN (Atypical cells glandular cells favouring neoplasia), adenocarcinoma in- situ (AIS), squamous cell carcinoma, adenocarcinoma	Immediate evaluation by colposcopy/biopsy (within 2 weeks) and treatment planning in the next two weeks
4	HPV Test positive	VIA/Cytology – if either positive referred for colposcopy **or** HPV 16, 18 Genotyping HPV 16, 18 negative, repeat HPV testing after one year HPV 16, 18 positive women should have colposcopy in 3 months

VIA positive cases

With the current pandemic and suspension of routine OPD services and outreach camps the opportunity of performing VIA becomes limited but opportunistic screening in all health facilities may continue with necessary precautions. If screening has occurred in the past and the patient has a VIA positive report it may be managed by ablative therapy if the criteria for ablation are fulfilled as per Government of India guidelines[2] (Appendix 1). Colposcopy and biopsy should not be delayed in women with a suspicion of invasive cancer (within 2 weeks). Once the pandemic is over, screening with VIA should resume in all primary health centres as per the Government of India Guidelines[2]

Management of preinvasive disease

With elective surgery being suspended, management of preinvasive disease is dictated by risk of progression. Some women may need to be scheduled for an excision /ablative procedure (high grade disease). Ablative procedures in those fulfilling criteria for ablation may be done with thermal ablation/cryotherapy as per availability. Women with an invasive cancer will need staging and treatment planning. (Table 2)

Women with CIN1 can be called in12 months for an HPV test/Cytology. Women with CIN 3 should be treated as soon as possible (Table 2)

Table 2: Management based on histopathology report

Histopathology report	**Management**
Cervical Intraepithelial neoplasia (CIN1)[8] (if the preceding smear is ASC-H or HSIL-a histopathology review is needed)	a) Follow up in 12 months
Cervical Intraepithelial Neoplasia (CIN 2 and CIN 3)	Treatment should be provided as early as possible
Invasive Cancer Early stage cervical cancer[10]	If surgical services are available, proceeding with standard-of-care is recommended. If access to surgery is limited, she may be referred to centres offering surgical services/radiotherapy.
Locally-advanced disease[10]	Chemoradiation with hypofractionation (increasing dose per day and reducing the number of fractions) to reduce the number of hospital visits

Management of Invasive cancer

There have been a number of guidelines and statements released since the pandemic on treatment of cervical cancer and follow similar principles. It has to be understood that invasive cancer patients will need treatment and should be strategized as soon as histopathological diagnosis is available. A treatment plan including staging and investigative work-up must be in place within 2 weeks. Surgical treatment with curative intent depends on the stage and availability of cancer centres doing oncosurgery during the pandemic. Surgery for Stage IA1 (microinvasive cancer) may be delayed for 8 weeks considering slow rate of growth[15]. This can be decided on the COVID situation in a particular area. For patients with Stage IA2, IB1-2, II A, radical surgery can be planned within 6-8 weeks[10,17]. These patients can also receive definitive chemoradiation if surgery is not possible considering the current COVID situation in a particular area. Patients with locally advanced and advanced cancers need chemoradiation with hypofractionation techniques (increasing dose of radiation and decreasing number of fractions). Whatever be the plan, patient anxiety must be addressed, counselling done and every effort made for referrals and treatment within a stipulated time.

General measures to be followed during screening and other diagnostic services

1. All women coming to the clinic should first be screened for symptoms or signs of COVID-19, including fever, respiratory and/or gastro-intestinal symptoms, and also checked for place of residence, whether a known hotspot area or containment zone. All COVID-suspect cases should be directed to the emergency room/ respective clinics for evaluation and management. Screening and diagnostic procedures may be deferred in these individuals.
2. All health care providers should wear appropriate PPE and patients should be given a mask to wear during consultation and examination.

3. Hands should be cleaned with soap and water or hand sanitizer that contains at least 60% alcohol before and after examining the patient. Recommended social distancing to be maintained in waiting areas (6 feet/2 metres)
4. Disinfection of the clinic and OT area is to be done at regular intervals as recommended[4]
5. All diagnostic procedures including colposcopy, biopsy, ablative procedures, and LLETZ, should be performed in outpatient settings. A negative COVID test report preferably RT-PCR is desirable 72 hours before the procedure. She should also self-isolate at home for at least two weeks prior to procedure. A serviced smoke extractor preferably with HEPA filters must be used for LLETZ procedures considering the theoretical risk of transmission by aerosolised particles
6. The minimum number of staff should be present during procedures.
7. Only one attendant/family member can accompany the patient
8. Details of OT set up with air conditioning requirements are available in the Indian Society of Anaesthesiology position statement[18]. The main principle would be to not allow virus laden particles out of the OT in which a COVID positive patient is being operated and at the same time keep viral load low in the OT by disinfection of surfaces as per protocol. OT should have its own ventilation system with an integrated high-efficiency particulate air filter (HEPA). Room AC's with exhaust fans and a fan blowing in air and a window kept slightly open also will work.[18]
9. Traffic and flow of contaminated air should be minimised by locking all doors of the OT during surgery, with only one possible route for entry/exit via the scrub room.
10. All electronic gadgets like pagers, laptop or mobile and hospital case sheets should be left outside the OT. Disposable pens are to be used if available.

Conclusions

The COVID-19 pandemic has pushed back cervical cancer screening programs, which had gained momentum in the previous years, to a virtual standstill. We need to re-think vaccination and screening strategies as outlined above with an expedited need to treat high grade lesions and suspect invasive cancers. This has also been an opportunity to introduce telemedicine and telehealth into screening practice and will allow women remain in contact

with the health care system. Self-sampling for HPV testing must be explored and a liaison with the pathologist and community health workers developed. Visual Inspection testing with proper patient and physician safety can be carried out in places where the COVID cases are on the decline. Finally, OT protocols for adequate ventilation and mitigating viral load must be considered.

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Appendix 1

Eligibility for Cryotherapy/Thermal ablation	Cryotherapy /Thermal ablationnot recommended in
The lesion should not be spread over more than 3 quadrants of the cervix	Postcoital bleeding
The TZ type should be type I. The entire lesion is located in the ectocervix with no extension to vagina/and or endocervix	Postmenopausal bleeding
The lesion is visible in its entire extent	Overt cervical growth
The lesion can be adequately covered by the largest available cryotherapy probe	Irregular surface
There should be no suspicion of invasive cancer	Bleeds on touch

Follow -up by VIA is recommended 1 year following cryotherapy/Thermal ablation