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NEWS LETTER

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Message

Dr. Anita Singh
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2020

It gives me immense pleasure to send my message for this FOGSI Oncology Committee news letter. Dr. Bhagyalaxmi has been a wonderful chairperson in present FOGSI team. I am personally involved with all her activities for almost one year now. She has organized several very high quality webinars with both national and international speakers of repute. Many important topics in Gynaecologic Oncology, from prevention to management has been discussed and newer developments in this field has been discussed in these webinars.

This is yet another attempt on the part of Dr Bhagyalaxmi Nayak to bring about this newsletter to the forefront of FOGSI for the benefit of our members with topics written by experienced and acknowledged writers.

I will like to bring to your notice the FOFSI's cancer screening event that we did on International Women's Day- 8th March 2020 with Oncology committee, my CSR activity as VP FOGSI 2020.Once I was allotted this activity, I felt it a challenging task ,but with help of FOGSI force with me I sailed through it very successfully.

"IT ALWAYS SEEMS IMPOSSIBLE UNTIL IT IS DONE"-Nelson Mandela
We could do it and we screened about 40,000 police women on that day. Congratulations to FOGSI and gratitude to all the participants of this mega screening venture.

In spite of passing these days through a bad phase of time, we FOGSIans are working hard for the, betterment of our women at the ground work level and towards our own academic progress,which will further continue.

"Be strong now,because things will get better

It might be stormy now,but it can't rain forever"

BE SAFE,BE STRONG,BE HEALTHY

LONG LIVE FOGSI

Dr. Anita Singh
Vice President, FOGSI, 2020

Dr. B. L. Nayak

Acknowledgement

Greetings from Oncology Committee FOGSI.

All are testimony to the fact that this has been a very very happening year for FOGSI. The pandemic has not been able to deter an iota of enthusiasm, which is a hall mark of FOGSI. Oncology Committee is also racing fast to keep up with the virtual tsunami that has flooded the FOGSI armamentarium. FOGSI oncology committee under the able guidance of FOGSI President ,Dr. Alpesh Gandhi and Vice President Dr. Anita Singh and along with other committees spearheaded the pan India screening programme for police women and was a huge huge success.

Before this a great initiative by immediate Past President Dr. Nandita Palshetkar of screening women in unreached areas of Assam, Arunachal Pradesh, UP, Chatisgarh etc. was successfully implemented with support of the life line express and was a first time experience for me as well. Hundreds of women were screened by FOGSI members of the respective local societies and the screening was done on the train itself which was stationed at each of the prior decided place. I extend my heart felt thanks to all the FOGSIANS who rendered their selfless service for the cause of women's health.

There has been too much of academic overflow and hope to see all this translate into patient care and more. In this news letter I've picked up two important and interesting topics by two stalwarts to address them. Wishing you a happy reading.....
Long Live FOGSI

Dr. Bhagyalaxmi Nayak
Chairperson,
Oncology Committee

SYNCHRONOUS VS. METASTATIC ENDOMETRIAL AND OVARIAN CANCER - A DIAGNOSTIC AND MANAGEMENT DILEMMA

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Synchronous and Metachronous malignant tumours are the two components of multiple primary malignant tumours (MPMTs) and the dilemma continues, as to how to differentiate primary from metastatic ones and consequently the management strategies. When the second primary cancer is diagnosed simultaneously or within 6 months of the primary cancer it is termed as Synchronous tumours and when diagnosed after 6 months of the primary cancer is defined as Metachronous tumors[1].Not very uncommonly, surprise detection of ovarian malignancy is found in a case of cancer of endometrium and vice versa. The coexistence of these malignant lesions at two sites can be either Synchronous primary endometrial and ovarian cancers (SEOC) or metastatic disease (MD) with either the endometrium or ovary being the primary site of origin[2]. The differential diagnosis between synchronous and metastatic diseases in endometrium and ovary do have prognostic and therapeutic implications, and often misdiagnosed as Stage III endometrial carcinoma or Stage II ovarian carcinoma.

PREVALENCE

SEOC is not very rare and accounts for 50-70% of all synchronous female genital tract tumors[3]. About 10% of women with ovarian cancers (OC) and 5% of women with endometrial cancers (EC) are diagnosed with SEOC[2].

PATHOGENESIS

Exact pathophysiology of SEOCs is unclear. Certain factors have been postulated like:

- Estrogenic environment - presence of estrogen receptors in both the sites.
- Secondary Mullerian origin - embryologically similar, so affected by hormonal stimulation and carcinogenic factors.
- Microenvironment restriction - reflects the low malignant potential of metastasis.
- The histopathology and epidemiological evidence demonstrates a strong association between endometriosis and ovarian cancer.

It is also possible that synchronous presence of these cancers is an indicator of an etiologically distinct condition. Perhaps patients have a more fragile genome and prior genetic damage may predispose to synchronous cancers. Thus, embryologic, hormonal or other phenomena may be associated with the development of malignancies arising simultaneously in genital tissues[4].

ASSOCIATION WITH ENDOMETRIOSIS

There is growing evidence that ovarian endometrioid carcinomas arise from transformed endometriosis; thus, endometrial and ovarian endometrioid carcinomas evolve from the same precursor endometrial epithelial cells5. The presence of endometriosis is associated with an increased risk of synchronous primary neoplasms mainly in ovary and endometrium. A hormonal field effect has been described for the development of these SEOCs supporting the theory of oestrogen receptors in the involved organs in question. SEOC classified as independent tumours, using conventional criteria, represent mostly primary indolent endometrial tumours with spread to Fallopian tube and seeding of the implant into the ovary. This explanation is supported by the finding that SEOC tumours showed a lower frequency of ovarian endometriosis than sporadic ovarian endometrioid carcinomas6.

The possibility to discriminate preoperatively between synchronous primary cancers of the endometrium and ovary and endometrial cancer with metastasis to the ovaries could be relevant for the surgeon to counsel the patient and plan the best surgical treatment.

Indeed, in patients who wish to preserve fertility, preoperative suspicion of synchronous primary cancers of the endometrium and ovary at an early stage could support a strategy of a first-step fertility-sparing surgery.

DIAGNOSIS

Simultaneous detection of malignancy at endometrium and ovary often challenges the clinicians and pathologists to make correct diagnosis and arrange appropriate managements. The distinction between independent primary tumors and metastasis from one site to the other is clinically significant but complicated as well. These two possibly can be distinguished, only after histopathological examination of surgical specimen[7], utilization of criteria set by Ulbright and Roth[8],later modified by Scully et al.[9] and immunohistochemical studies10. Moreover, molecular diagnostic methodology has been integrated to differentiate synchronous from metastatic cases of SEOC11.

Histopathological Diagnosis- is generally made by histopathologic evaluation of both the tumours following the age- old two criteria as below.

- Ulbright and Roth (1985)
- Young and Scully (1998)

Ulbright and Roth criteria[8]- 1 major or 2 or more than 2 minor criteria

MAJOR

Multinodular ovarian pattern

MINOR

1. Small ovaries<5 cm
2. Bilateral involvement
3. Deep myometrium invasion
4. Vascular invasion
5. Tubal lumen involvement

Absence of these criteria leads to the diagnosis as independent tumors.
Scully et al[9]. described a list of criteria based on postoperatively analysed features to differentiate SEOC from metastasis.

Number	Primary Endometrial Cancer with ovarian metastases (ECOM)	Primary Ovarian Cancer with endomentrial metastatses (OCEM)	Independent Primary Endomentrial and Ovarian tumors (SEOC)
1	Histologic similarity of the tumours	Histologic similarity of the tumours	Histologic dissimilarity of the tumours
2	Large endometrial and small ovarian tumours	Large ovarian and small endomentrial tumors	
3	Atypical endomentrial hyperlasia additionally present	No atypical endomentrial hyperlasia	Atypical endomentrial hyperlasia
4	Deep myometrial invasion. Direct extension into adnexal. Vascular space invasion in myometrium, surface implant or combination in ovary	Location in ovarian parenchyma. Direct extension from ovary into outer wall uterus. Ovarian tumor located in parenchyma	No or only superficial myometrial invasion of endometrial tumor. No vascular space invasion, surface implants or predominant hilar location in ovary. Ovarian tumor located in parenchyma
5	Spread elsewhere in typical pattern of endomentrial carcinoma.	Spread elsewhere in typical pattern of ovarian carcinoma	Absence of other evidence of spread of ovarian tumor.
6	Ovarian tumour, Bilateral and/or multi-nodular	Ovarian tumour unilateral(80-90%) of cases in a single mass	Ovarian tumour unilateral (80-90%) cases
7	Ovarian endometriosis absent	Ovarian endometriosis absent	Ovarian endometriosis absent
8	Aneuploidy with similar DNA indices or diploidy of both tumours*	Aneuploidy with similar DNA indices or diploidy of both tumours*	Different ploidy of DNA indices, if aneuploidy of the tumours*
9.	Similar molecular genetic karyotypic abnormalities in both the tumours	Similar molecular genetic karyotypic abnormalities in both the tumours	Dissimilar molecular genetic karyotypic abnormalities in both the tumours

ECOM- Endometrial Cancer and Ovarian Metastases, OCEM- Ovarian cancer and Endometrial Metastases, SEOC- Synchronous Endometrial and Ovarian Cancer, * The possibility of Tumour heterogeneity must be taken into account in evaluation of ploidy findings.

Specifically, distinguishing SEOC from metastatic ovarian cancer to the endometrium (or metastatic endometrial cancer to the ovary) has long been challenging, especially if the histologic type is concordant in the two cancer sites such as endometrioid tumors. It is observed that the histologic subtype of both primary tumors is endometrioid in 50-70% of cases with SEOCs[3]. However, synchronous primary endometrial and ovarian cancers may have a similar appearance or may be of different histologic types[3].

Grade and stage of the diseases at both the sites are utilised to differentiate between synchronous and metastatic disease. Size and grade of the tumour, depth of myoinvasion, direct adnexal extension, lymphovascular space invasion, presence of atypical hyperplasia are the criteria considered in case of endometrial carcinomas and the presence of endometriosis, size and laterality of the tumor, surface implants, hilar location, lymphovascular space invasion, and multinodularity are the factors considered in cases of ovarian tumors. In other words SEOCs are characterized by histological dissimilarity of the tumors, no or only superficial myometrial invasion of endometrial cancer, no vascular space invasion of endometrial and ovarian tumor, absence of other evidence of spread, ovarian unilateral tumor, ovarian tumor in the parenchyma and without involvement of the surface of the ovary, dissimilarity of molecular genetics or karyotypic abnormalities in the tumors, and different ploidy of DNA of the tumors. It is confirmed by several studies that, low stage (organ confined) and low-grade SEOs behave clinically as independent primary tumors. In case of uncommon histologic features like grade 3, clear cell carcinoma, raises suspicion as to diagnosis of SEOC.

MOLECULAR IMMUNOHISTOCHEMICAL STUDIES

Several molecular studies have been done to characterise SEOC and most have shown that 95% of SEOC share clonal origin irrespective of their clinic-pathological features. So, from this point of view the benefit of molecular analysis is disputable.

The most common mutation identified is a PTEN (over 75% cases) followed by ARID 1A.Other less commonly identified mutations were PIK3CA, HNF1B, KRAS, CTNNB1[10].

There is evidence of clonal relationship which suggests that most SEOCs are metastatic disease from either endometrial or ovarian primary tumours or not dual primary cancers but numerous reports have pointed to their favourable prognosis despite having metastatic disease, because of the fact that disseminating cells at either site remain indolent and lack capacity for further dissemination[11].

Use of CK, Vimentin, CEA, CA125 and CA19.9 as other ancillary methods have been assessed by Prat et al in1991 to help in diagnosis but with overlapping results, hence was not found to be beneficial[12]. Halperin et al.2003 described that 62.5% of SEOC can be classified by ER/ PR status and 31.3% by Bcl-2 detection[13].Desouki et al. 2014 observed that vimentin was negative in 97% of primary ovarian carcinomas and positive in 82% of primary endometrial carcinomas. The expression in SEOC was discordant in 53% cases14. However, the practical utility of IHC in the light of recent clonal origin of SEOC is disputable and can also be influenced by the tumour microenvironment[10].

ASSOCIATION WITH LYNCH SYNDROME

SEOC is a disease of middle-aged women. One hypothesis to link this association is the possibility of Lynch syndrome15. The mean age of endometrial cancer diagnosis in women with Lynch syndrome is in the late-40s (47-49 years) and the mean age of ovarian cancer in women with Lynch syndrome is also in the 40s (42-49 years). Moreover, the incidence of synchronous endometrial cancer in ovarian cancer among women with Lynch syndrome is reported as 21.5%. Microsatellite instability has been reported to be present in 40% of women with SEOC in few case series16. So, genetic assessment and testing is highly recommended for women with SEOC.

MOLECULAR ANALYSIS REVEALS[17]:

i) Almost all SEOCs are of clonal origin and even low stage and low-grade tumours seem to represent dissemination from one site to the other (however, without a possibility to conclusively assess the directionality).

ii) All sporadic SEOCs shared non-synonymous mutations in at least one cancer driver gene of EEC and/or EOC.

iii) There were striking similarities between the molecular profiles from the SEOC subgroup and the TCGA 2013 endometrial Carcinoma rumour set, implying the endometrium could be the primary origin for these cases and not the ovary.

iv) TP 53 mutations and the presence of extra-uteroovarian disease were associated with poor outcome.

Recent studies show that the concordance rate between histopathologic diagnosis and molecular diagnosis was considerably low, and it may be possible that the cases that met the diagnostic criteria for SEOC were actually metastatic endometrial cancer to the ovary or vice versa11, [18]. As evidenced, no single diagnostic criteria is perfect in terms of differentiating between primary and metastatic disease, it is mandatory to integrate all available clinicopathological, immunohistochemical and molecular data in the assessment of problematic diagnostic cases of synchronous carcinomas, as proper diagnosis is essential to decide upon the extent of surgical treatment, adjuvant therapy and prognosis[19].

PATIENT CHARACTERISTICS:

It is observed that the incidence of SOEC is about 19% in women aged < 50 years and 25%of women aged 25-45 years. The involved ovaries are normal on preoperative clinical and radiological assessment in 15% of cases. The women are nulliparous in about 40% cases, 2/3rd of the cases are premenopausal and 1/ 3rd are obese[20, 21].

Usually the common presenting symptoms of SEOC are abnormal uterine bleeding in about 46% cases and few with postmenopausal bleeding. About 17% of women patients with pelvic pain and/13% with palpable abdominal mass.

MANAGEMENT

FERTILITY SPARING SURGERY (FSS):

As the disease is commonly encountered in early age, the issue of FSS needs to be considered and discussed. Whenever FSS is considered in either early ovarian or in endometrial carcinoma, thorough evaluation (with biomarkers and imaging examination) should be done to exclude the presence of malignancy in other site to rule out synchronous or metastatic disease in other organ in question[21]. Moreover, when ovarian conservation in endometrial carcinoma is an issue, thorough careful assessment of adnexae is recommended to rule out presence of malignancy in ovary(s).

The FSS can be offered to some early cases of SEOC with certain histologic profiles in early stage and low grade tumours both the sites after discussion about the risk of recurrence. Successful pregnancy outcome has been achieved in a 25 yrs old woman with SEOC, as reported by Atallh et al. in 2013[22].

SYSTEMATIC SURGICAL STAGING :

When FSS is not an issue, the treatment of choice in SEOC is systematic surgical staging. The procedure includes: total abdominal hysterectomy with bilateral salpingo-oophorectomy, total omentectomy, appendectomy, pelvic and para-aortic lymphadenectomy± appendicectomy and complete resection of all disease after collecting ascetic fluid/saline wash fluid for cytology. Although it is not always possible to identify SEOC and ECOM/OCEM intraoperatively, lymph node dissection should be performed in every SEOC

patient. This procedure allows a more clear decision for stage related postoperative adjuvant therapy[2, 4]. Supracervical hysterectomy should be avoided in carcinoma of ovary, as considerable fractions of women with epithelial ovarian cancer may have concurrent endometrial cancer and by doing so, disease left in the cervical stump may result in recurrence. If at all supracervical hysterectomy for ovarian cancer is planned, preoperative assessment of endometrial pathology may be a reasonable approach to rule out synchronous endometrial cancer [23, 24].

ADJUVANT THERAPY:

After surgery every effort should be employed to differentiate primary from metastasis, to plan adjuvant therapy. In patients with SEOC <40 years of age, endometrial cancer component presents at an earlier stage, lower grade, smaller tumour size, no or less myoinvasion, and negative lymphovascular invasion and the ovarian counterpart in such situation do have similar favourable histopathological features. Adjuvant therapy is avoided in such early confined disease in young and they do have considerably equal survival benefit in comparison to disease confined to endometrium only[25]. In other words, women with stage I endometrioid endometrial cancer with synchronous stage I endometrioid ovarian cancer have a survival outcome similar to those patients with stage I endometrioid endometrial cancer without synchronous ovarian cancer. When compared to primary epithelial ovarian cancer without synchronous endometrial cancer, SEOC was associated with better cause-specific survival (CSS) if ovarian cancer is endometrioid type or if endometrial cancer is endometrioid type[26]. SEO-EC localized to the uterine body and adnexae may have low risk of recurrence, although it is defined as metastatic disease by next generation sequencing (NGS).Adjuvant therapy may result in unnecessary treatment for SEO-EC patients whose disease is localized to the uterine body and adnexae with endometrioid histology.

The European Society of Medical Oncology (ESMO) and the National Cancer Center Network (NCCN) guidelines recommend adjuvant therapy for patients that have endometrial cancer with ovarian metastasis or ovarian cancer with uterine metastasis [27, 28].Patients with advanced stage and grade of the diseases or with non-endometrioid histology, and features suggestive of metastatic disease, require a more aggressive management with postoperative adjuvant chemotherapy and/ or radiotherapy[18].The most active chemotherapeutic agents are: taxanes, anthracyclines and platinum compounds.

The choice of adjuvant therapy (Chemotherapy, radiotherapy or both) depends mostly on the primary organ of origin. For example, in stage III endometrioid carcinoma of endometrium (Ovarian met is regarded as stage IIIA) is best treated by Chemotherapy with concurrent chemo-radiotherapy, whereas adjuvant treatment of choice of stage II ovarian carcinoma (when ovarian carcinoma involves uterus) is systematic chemotherapy.

PROGNOSTIC FACTORS:

Yoneoka Y et al in their retrospective study commented that prognostic factors of SEO-EC may differ from the established prognostic factors of endometrial and ovarian cancer[29].

Their observation was:-

1. Confined lesions in uterine body and adnexa with complete surgical resection did have favourable prognosis with longer 5 year progression free (PFS) and overall survival (OS).
2. Patients with lymph node metastases had significantly lower PFS than patients without lymph node metastases
3. Cervical stromal invasion was a poor prognostic factor
4. Myometrial invasion of ?1/2 and LVSI tended to have worse PFS
5. MMR protein status was not significantly associated with the survival

However, advance stage of the disease and non-endometrioid histology carries a poor prognosis.

PROGNOSIS

Several studies have shown that patients with synchronous primary cancers have a good overall prognosis. On univariable analysis it was observed that women with SEOC had a 10-year CSS similar to those who did not have synchronous ovarian cancer (79.4% versus 80.7%) and patient with endometrioid histology in the two cancer sites had a higher 10-year CSS compared to those without synchronous ovarian cancer (88.7% versus 80.7%) 30.The Gynecologic Oncology Group (GOG) study found that women with synchronous primary endometrial and ovarian cancers had an overall prognosis of 86% 5 year survival and 80% 10 year survival[2].

Conclusion

The most frequently documented synchronous malignancies are those of the ovary and endometrium. The diagnostic dilemma of Synchronous primary endometrial and ovarian Cancer vs metastatic disease remains and separating the two groups is utmost important as the prognosis is different. Additionally, they are more frequently undiagnosed or under staged due to limited preoperative work up and also intra- operative assessment of ovarian pathology is fallible especially with occult disease. Despite sharing clonality as suggested by molecular studies, SEOC are diagnosed at a younger age and have a much better prognosis than metastatic disease. NGS is an important tool for the management of these lesions for use in future targeted therapies.

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RCOG, Calcutta

Oncology Workshop, Dhaka

Cervical Cancer screening programme in Lifeline Express

Camp in a Urban slum

International Conference on Endometriosis

USE OF HPV TEST IN PRIMARY SCREENING FOR CERVICAL CANCER

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INTRODUCTION

Cervical cancer screening programmes started with regular Pap screening as the primary test. HPV tests were initially introduced as triage tools for cases diagnosed as ASCUS on Pap smear. Subsequently the superiority of HPV test as screening due to far greater sensitivity was established and it was included in co-testing strategies. Recently, a quantum shift has occurred and HPV testing is widely accepted as the primary testing modality for cervical cancer screening.

HISTORY

The "PAP Test" was developed by Dr. George N. Papanicolaou (1883-1962) born in Greece. In the year 1920, he began to his work on the cytopathology of the human reproductive system. He was able to discern differences between the cytology of normal and malignant cervical cells through a simple viewing of swabs smeared on microscopic slides. Although his initial publication of the finding in 1928 went largely unnoticed, later on, he collaborated with Dr Herbert Traut, a gynaecological pathologist, eventually publishing their landmark book in 1943, "Diagnosis of Uterine Cancer by the Vaginal Smear" (1). It described physiological changes of the menstrual cycle and the influence of hormones and malignancy on vaginal cytology. The simple procedure, now famously known as the Pap smear, quickly became the gold standard in screening for cervical cancer as regular Pap smear screening in 3-5 yearly intervals reduced mortality by 70%. Although George Papanicolau did not receive the Nobel prize for his very important discovery, the Nobel prize in Physiology or Medicine for 2008 was awarded to Harald zur Hausen for his discovery of the role of human papilloma viruses (HPV) in causing cervical cancer. Harald zur Hausen went against current dogma and postulated that oncogenic HPV caused cervical cancer, the second most common cancer among women. He realized that HPV-DNA could exist in a non-productive state in tumours, and should be detectable by specific searches for viral DNA. He found HPV to be a heterogeneous family of viruses. Only some HPV types cause cancer. His discovery led to characterization of the natural history of HPV infection, an understanding of mechanisms of HPV-induced carcinogenesis and the development of prophylactic vaccines against HPV acquisition.

Looking at the progress in our understanding and implementation of cervical cancer prevention, the fact that cervical cancer is sexually transmitted was documented in the year 1850 by Rigoni-Stern; the Pap test was developed in the year 1928, and Pap screening clinics were established in the 1940's in the UK and USA. Screening guidelines were laid down in the1980's. The detection of HPV in cervical tumour in zur Hausen's lab in 1983 led to the production of HPV virus like particles in 1992 and introduction of HPV vaccines in 2006; development of HPV tests and introduction of HPV testing in screening guidelines. We have come a long way towards prevention and elimination of the disease.

HPV AS PRIMARY SCREENING TEST

HPV test has the highest sensitivity to detect high-grade cervical intraepithelial neoplasia (CIN2+). Advantages of the test are that it is not subjective, can be automated, centralized and better quality controlled with a high throughput and results are highly reproducible because the test is less dependent on training of lab personnel. A meta-analysis by Cuzick et al on studies from Europe and USA in the year 2006 showed a sensitivity of 96.1% for HPV test whereas cytology had a poor sensitivity of 55%. The authors also reported the incidence of cytology and HPV positivity at all ages (~ 5-15%) (2). According to the World Health Organization International Agency for Research on Cancer (IARC), prevalence of HPV positivity around the globe ranges from 8% to 25%. Age-specific HPV prevalence among women with a normal cytology was found to be >10% below thirty years of age and <10% beyond thirty years of age in a meta-analysis by Burchell et al in 2006. Therefore the age group for primary HPV testing was suggested as 30 years and above (3). In a cross-sectional study by Bhatla et al in north India on 524 women, the prevalence rates of HPV infection among women with normal, low-grade cervical neoplasia (CIN 1) and high-grade CIN (>CIN2) were found to be 7.6%, 42.3%, and 87.5%, respectively (4).

Several large scale randomised controlled trials (ARTISTIC, POBASCAM, NTCC, SwedeScreen, CCCaST, India Screening trial, Finnish screening trial) have shown significantly better prevention of cervical cancer for women screened with HPV testing. In the year 2013, WHO guidelines for screening of cervical cancer also advocated that use of HPV test for primary screening and countries that have not already established cytology programs should not start to do so now. Primary HPV screening has a better performance than cytology in detection of glandular lesions.

HPV TEST AS A PART OF CO-TESTING

Schiffman et al quantified the relative performance of HPV and cytology components of co-testing in cervical screening and concluded that HPV testing identified more women subsequently diagnosed with cancer ($p < .001$) and precancer ($p < .001$) than cytology. HPV testing was statistically significantly more likely to be positive for cancer at any time point ($p < .001$), except within 12?months ($p = .10$). HPV negative/cytology positive results preceded only small fractions of cases of precancer (3.5%) and cancer (5.9%). Hence the contribution of cytology to screening translated to earlier detection of at most five cases per million women per year (5). Dillner et al in their multinational cohort study on 24 295 women showed a cumulative incidence rate of CIN3+ after six years to be considerably lower among women negative for HPV at baseline (0.27%, 95% CI: 0.12%-0.45%) than among women with negative results on cytology (0.97%, 95% CI: 0.53%-1.34%) suggesting that screening intervals could be safely increased to five years in women undergoing co-testing (6). Another meta-analysis by Tota et al in 2017 suggested that HPV testing is much safer than cytology and there is no additional benefit from co-testing compared with HPV testing alone.

HPV TEST VS VIA (VISUAL INSPECTION WITH ACETIC ACID)

In 2009, Sankaranarayanan et al in their landmark cluster-randomized trial on 131,746 healthy women between the ages of 30 and 59 years in rural india who underwent screening by HPV testing (34,126), cytologic testing (32,058), or VIA (34,074) or standard care (31,488, control group), found that in a low-resource setting, even a single round of HPV testing was associated with a significant reduction in the numbers of advanced cervical cancers and deaths from cervical cancer (HR 0.52; 95% CI, 0.33-0.83). Screening by VIA had a lower mortality reduction as compared to HPV testing (HR 0.86; 95% CI 0.60-1.25). Still one or two rounds of VIA testing remains the present reality for rural India (7). The development of rapid, affordable,

point-of-care HPV tests may make HPV testing a reality in future. It was hoped that careHPV would be the answer, but it is also quite expensive and is a batch test, which does not lend itself very well to a "screen-and-treat" scenario. Self-sampling may emerge as a solution for rural areas. Visual assessment for treatment (VAT) may eventually be used as an adjunctive for screen-and-treat with the HPV test.

HPV SELF-SAMPLING FOR HARD TO REACH WOMEN

HPV self-sampling is a process where a woman uses a kit to collect a (cervico)vaginal sample, which is then sent for analysis to a laboratory. HPV collection methods include lavage, brush, swab and vaginal patch. Several studies have shown linkage between self sampling and follow-up diagnosis and management. In a cross-sectional study on 546 women by Bhatla et al (2006), 98% women were able to provide a satisfactory self-sample, PCR detected oncogenic HPV in 12.3% of self- and 13.0% of physician-samples. Overall, 93.8% agreement between physician- and self-samples (k = 76.31%, 95% CI: 64.97-82.29%, p =.04). Sensitivity, specificity, PPV and NPV of both methods were similar (8). Self-sampling has high acceptability, participation rate, allows privacy, targets non-attendees and remote locations, improves performance of screening programs and has a high concordance with physician-collected samples.

SCREENING IN THE POST-VACCINATION ERA

Post-HPV vaccination, as lesion prevalence declines, PPV of both cytology and HPV testing will decline but performance of cytology is expected to be worse than of HPV testing. A modelling study by Franco et al suggests that for cytology, it could fall below 10% due to its subjective nature (9).

GLOBAL PROGRESS IN HPV TESTING

There has been a gradual increase in the number of countries implementing primary HPV screening in their national programs (Australia, United Kingdom, Argentina, Spain, Guatemala, Honduras, Italy, Mexico, Netherlands, Spain, Turkey, USA) as well as pilot programs (China, Colombia, El Salvador, Germany, India, Nicaragua, Paraguay, Peru, Republic of Georgia, Rwanda, Uganda, Kenya).

WHO CALL FOR ELIMINATION

In 2018, the WHO Director-General declared his vision of a world without cervical cancer as he gave a call to action to eliminate cervical cancer as a public health problem. The threshold is <4 cases per 100,000 women. Targets to be achieved by 2030 are:

- 90% of girls fully vaccinated with HPV vaccine by 15 years of age
- 70% of women screened with a high precision test (HPV or more effective test) at 35 and 45 years of age
- 90% of women identified with cervical disease to receive treatment and care.

Screening does not save lives, treatment of screen-detected lesions is critical. Single visit approach is to be encouraged. In low resource settings VIA is still recommended for screen-and-treat approach and colposcopy for a screen, see-and-treat approach. Portable colposcopes at last mile facilities can be used by health workers to capture and transmit images. Incorporation of AI for diagnosis is the new challenge - Automated Visual Examination (AVE).

CERVICAL CANCER PREVENTION DURING THE COVID PANDEMIC

Prevention services have taken a backseat. HPV testing by self-sampling is a good option. Screening visit appointments will have to ensure screening for Covid and social distancing - the "camp" approach is not appropriate presently.

CONCLUSIONS

Primary HPV testing has consistently proven better than other screening modalities. Screening can be initiated at a later age and screening intervals can be lengthened reducing the work load and cost in less developed regions. It allows improved detection of glandular lesions and is more accurate in elderly women. It is reproducible, automated and less prone for human error. The hunt is still on for a reliable, affordable, point-of-care HPV test.

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Cervical Cancer Elimination Day

PICSEP Workshop

Seminar for Rotary Club