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With the South African Society of Gynaecologic Oncology, Radiation Therapists, Oncology Nursing Society, Oncology Social Work Society, SA Medical Physics Society and South African Society of Oncology Pharmacists

1. Can cervical cancer be prevented in Africa?

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Cervical cancer incidence in Africa in 2008 was equivalent to the incidence in Scandinavian countries prior to the implementation of cytology based screening programmes in the early part of the 20th century. With the introduction of cytology based programmes the incidence of and mortality from cervical cancer fell substantially and today, in well organised screening programmes that function optimally, cervical cancer is a rare disease. Sub-Saharan Africa has faced many challenges in the past 300 years, not the least being the long term impact of colonialism, systemically racist governments and then post liberation, the legacies of poor governance, lack of financial, human and many other resources. Because cervical cancer is a largely preventable disease, coupled with an awareness that cytology based programmes are hard to initiate, implement or sustain, a concerted effort to find alternative screening tools and approaches has been attempted in the past 15 years. These studies have evaluated a range of alternative screening tests, including visual inspection methods which have involved thousands of women in Africa, Asia and Latin America. These studies have consistently shown the much greater sensitivity of molecular testing with Human papillomavirus (HPV) DNA testing compared to cytology, but with a lower positive predictive value and specificity. However, the near 100% negative predictive value makes it an ideal test for settings where women will be screened, if at all, only once or twice in a lifetime. The most critical factor in setting up secondary prevention for cervical cancer is the creation of an appropriate infrastructure and to provide adequate resources for the programme to function. Primary prevention of cervical cancer through HPV vaccination offers a whole new approach and opportunity to prevent cervical cancer by preventing infection with high risk types of HPV, known to be aetiologically associated with cervical cancer. However, implementing HPV vaccination is a relatively complex process in countries that lack immunisation

programmes for adolescent/pubescent children. Vaccination though has proved to be a very successful public health intervention and with the pressure of the Millennium Development Goals, population coverage with other types of vaccines has improved significantly in developing countries, reaching over 90% in many areas. Can cervical cancer be prevented in Africa? Yes it can, but whether resources will be allocated to these programmes will ultimately be decided by those in control of resources (usually politicians). A commitment and realisation from the governments of Africa that investing in the health of their women is cost-effective, reduces poverty, and uplifts the growth of nations at all levels. The MDGs have made women's health a priority. Cervical cancer fits into this paradigm.

2. A review of fertility-sparing treatment in gynaecological cancer

Koller AB

University of the Witwatersrand

Objectives: To review the current fertility sparing treatments in young women with cancer who are still desirous of having children and explore the historical events leading up to modern day treatments.

Design and method: A review of the relevant literature.

Results: A paradigm shift from radical fertility destroying treatment to the least effective fertility sparing treatment in gynaecological cancer is unfolding.

Conclusion: Fertility preservation is an exciting and challenging new field. The literature currently shows that some 40% of carefully selected patients suffering from early cervical, endometrial or ovarian carcinoma treated with fertility sparing methods have been able to give birth to a live child with less than 5% succumbing to their disease in later years.

Whatever the future developments in this field will be, it is clear that fertility preservation should be carefully considered in young patients undergoing treatment for gynaecological cancer.

3. Laparoscopic training in oncologic fellowship

Soliman PT

MD Anderson Centre, Houston, Texas, USA

With the increasing role of minimally invasive surgery in gynecologic oncology the importance of training the next generation in these minimally invasive surgical techniques has become critical. During this presentation we will discuss different modalities of teaching minimally invasive surgery including simulation and animal labs. In addition, we will review the experiences of several large fellowship programs and their incorporation of minimally invasive surgery into the fellow curriculum.

4. HPV vaccination: where do we stand?

Lindeque BG

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The availability of vaccines against high risk HPV types is regarded as one of the big developments of our time. Currently there are two vaccines available, one against HPV 16, 18 and one against HPV 16, 18, 6, 11. The estimate is that vaccination of a female child around puberty will protect up to 75% of vaccinated persons from developing cervical cancer in later life. Vaccines are safe, contain no live viruses, and may have cross protection against other HPV strains as well.

The factors in favour of including HPV vaccination in the EPI in South Africa are:

- To the best of current knowledge a 100% prevention rate
- Excellent safety profile
- Additional effectiveness against HPV strains causing genital condylomata.

The factors against such policy are:

- Costs: the vaccines will have to be purchased
- Setting up a vaccine cold chain and distribution system.

Factors still under debate are:

- Vaccination of HIV infected persons
- Vaccination of boys
- Longevity of the immunity
- The length of the “catch up” immunisation of girls older than the target group.

Current policy proposals for the public sector include:

- Vaccination of all girls between 9-12 years
- Three doses to be given as per product schedule
- No difference between HIV infected and non HIV infected persons (except for children with AIDS)
- Screening required in later life.

Ethical issues that need to be resolved would be consent, marginalisation of those who decline vaccination, and the practicalities of HPV vaccination in the school milieu. For the private sector the vaccine is as much a commodity available as so many others. The same age recommendations are valid, more boys are likely to be vaccinated, and the later surveillance is the same. The proposal for managing the vaccination as part of the EPI and school system will be addressed during the presentation.

5. A practical approach to screening for cervical neoplasia

Adam Y

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Population based screening and treatment programs of pre-malignant lesions of the cervix has significantly reduced the morbidity and mortality associated with cervical cancer, with reductions in deaths of between 45% and 80%. The SA government introduced the National Screening program for the prevention of Cervical Cancer, using the WHO recommendation for middle income countries. The WHO recommendation was that, when 80% of women have been screened, the interval should be between 5 and 10 years, as resources permit. In SA an interval of 10 years has been advocated for the present. The South African program aims at achieving a wide coverage and in earlier presentation. For cervical cancer prevention strategies to be effective all aspects of a screening program needs to be pursued; screening, referral and diagnosis, treatment and follow-up. I will only discuss screening and attempt to make sense of the following:

- Where are we with screening at present in SA?
- Is Pap smear screening the best for SA?
- Age to commence and stop screening? Symptomatic screening.
- Coverage vs. intervals of screening: when to repeat the test?
- Liquid Pap vs. conventional Pap: when to add HrHPV testing?
- Screening in HIV infected women?

6. Screening and LLETZ: is colposcopy really necessary?

Botha MH

Stellenbosch University

Screening with cervical cytology implies further investigation and treatment in case of an abnormal smear. It has become common practice to offer excision treatment at the first abnormal smear and the obvious risk of overtreatment exist (Chia 1994).

LSIL regress in up to 50% of patients (Robertson 1988).

Even in those with CIN III only 36% will develop invasive cancer during 20 year follow-up (McIndoe 1984).

LLETZ procedures are associated with bleeding (2-5% requires packing and 0.5% transfusion) (Lopes 1992). The risk for premature delivery is significantly higher after LLETZ (2.07 [CI 1.88 – 2.27], Noehr 2009) (OR 2.61 [CI 2.02 – 3.20] Jakobsson 2009).

Colposcopy has a role to see the location of the abnormalities, to exclude cancer, to diagnose infections and importantly to guide treatment. It plays an important role to identify only the abnormal areas which need excision.

One-step treatment is only recommended if there is HSIL on cytology combined with colposcopic abnormalities on the cervix that support the diagnosis. There should be no evidence of invasive carcinoma (Lindeque 2005).

7. Should we use liquid-based cytology?

Snyman LC

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Conventional cytology (CC) has been used for many years as an option in the secondary prevention of cervical cancer and in countries with formal implemented population based cervical cancer screening it has reduced the incidence of the disease by up to 70%. In recent years liquid based cytology (LBC) has become available as an alternative to conventional cervical smears. In many countries LBC has replaced CC smears as the screening method of choice.

Both methods are acceptable to use. In women with blood or inflammation LBC probably provides better specimen adequacy. Both methods perform equally well for detection of HSIL, while LBC is better in detecting glandular abnormalities, ASCUS and LSIL. Reflex HPV testing is possible with LBC without the necessity to obtain a second specimen for this purpose.

Several factors play a role when comparing cost effectiveness between CC and LBC. In addition the increased detection of ASCUS and LSIL might add to extra investigations in conditions not that clinically important. Cost effectiveness should be considered within the context of the health system LBC is used in.

8. Is cancer on the increase worldwide?

Soliman PT

MD Anderson Centre, Houston, Texas, USA

While surgical techniques, chemotherapy and radiation

therapy have continued to evolve over the last several decades, the incidence of cervical cancer is the only gynecologic cancer that has significantly declined as a result of cervical cancer screening, in countries where screening is available. The incidence and mortality of both endometrial and ovarian cancer cases has slightly increased. During this presentation we will discuss the risk factors for these cancers and potential prevention strategies.

9. Human papillomavirus: association with cervical cancer

Dreyer G

University of Pretoria

Introduction: Accurate current knowledge of the genital hrHPV prevalence in different developing countries is essential for cost analysis and planning for regionally tailored national prevention and screening programmes.

Epidemiology: Cervical cancer develops as a consequence of infection with oncogenic human papilloma virus (HPV). Various co-factors play a role in the persistence of the infection and in the development of invasive cancer. In South Africa and sub-Saharan Africa co-infection with HIV and the associated immune-depletion is without doubt the most dramatic and influential. The influence of a high prevalence of untreated HIV infection in the population is expected to influence the epidemiology of HPV and may influence the type distribution not only in the general population but also among cervical lesions.

HPV epidemiology in Africa and South Africa: Regional differences exist in HPV infection and both local prevalence and type distribution are highly relevant factors to take into account in the development of cervical cancer prevention programmes. In contemporary local data collected among women of reproductive age and from a population with a high prevalence of HIV infection, the prevalence of pre-invasive disease (HSIL) was found to be 11.2% in women 35 and younger, and 7.3% in women >35 years. The incidence of hrHPV infection was 55.3% for the group (65% in women 35 and younger, 50% in women >35).

HPV types in cervical cancer: Worldwide the most common eight HPV types found in association with cervical cancer remains more or less constant and are generally quoted as HPV types 16,18,31,33,35,45,52 and 58. The most striking difference in South African and African data is that type 35 is much more common than in Western and Asian countries and is associated with up to 10% of cases. Types 31 and 58 are less frequently encountered and type 52 is of more importance than in other regions.

In a local study using RNA and DNA analysis of biopsy material, one of these eight most common oncogenic types were responsible for at least 159 of the 183 cases. An additional six tumours contained multiple types from this group. These tumours are almost definitely caused by one of more of the same group of viruses, although the specific type could not be confirmed. In this study 90.2% of cervical cancers were caused by HPV alpha virus numbers seven and nine, while only 4.4% are probably caused by HPV types from other alpha species including alpha five, six and eleven. Eight tumours (4.4%) could not be explained at all using the specific technology and conditions.

Conclusion: The epidemiology of HPV in the general population and in women with pre-invasive disease is of huge importance to calculate the effect of different screening and vaccination options. Of even greater importance is local data reflecting common true carcinogens in our unique population.

10. Surgery for uterine sarcoma

Botha MH

Stellenbosch University

Uterine sarcomas often highly malignant and comprise 3% of all uterine malignancies. The 3 most common types (90% of the total) are carcinosarcoma (MMMT), leiomyosarcoma and endometrial stromal sarcoma. FIGO changed the staging of sarcomas in 2009 to guide management and diagnosis.

Carcinosarcoma is usually managed by simple hysterectomy with proper washings and adnexectomy. Systematic pelvic (and perhaps para-aortic) lymph node dissection is essential but it is still unclear whether lymph node dissection improves patient survival (Nam 2011).

Leiomyosarcoma is treated by simple hysterectomy due to low risk for ovarian metastases (salpingo-oophorectomy not essential). Lymph node dissection is not indicated. I case of isolated lung metastases surgery may play a role.

In the management of endometrial stromal sarcoma, lymph node dissection not recommended in apparent early disease due to low risk for metastases (only 5,5% in 1708 cases) (Nam 2011).

Complete surgical resection is the only curative treatment modality for uterine sarcomas.

11. HPV alpha species nine and seven: changed distribution patterns of genotypes

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Objective: HPV type-distribution appears to be regionally different and may be influenced by population related factors over time. We studied the HPV types in the general population and in cervical cancer specimens of the same peri-urban population in Tshwane, South Africa.

Method: Cervical samples from 1000 women in the population were tested for high risk HPV DNA. In addition 150 cervical cancer samples were collected from the same population and tested for the same viral types using DNA and RNA analysis. The viral type distribution was determined in both samples and compared. In addition the type distributions were compared with data reported from meta-analysis of African studies.

Results: The sequence of HPV genotypes of the alpha species 9 in the population was 16, 58, 33, 35, 52 and in cervical cancer was 16, 35, 33, 52, 31. HPV 35 was present in 8,4% of women, but in 16% of cervical cancer specimens, while type 51 was present in 13% of the population but less than 1% of cancers. HPV 45 and 18 (alpha species 7) was present in 10% and 9% of the population while it was causative of 10% and 14% of cervical cancer cases.

Discussion: HPV types 35 and 52 are over-represented in cervical cancer in our region and type 45 appears to gain increasing importance as an oncogene. Type 51 was shown to have low oncogenicity and should probably be re-classified.

12. A pilot study comparing 3D ultrasound, MRI and frozen section in myometrial involvement in endometrial cancer

Dumbrill D, Whitaker J, Levy A, Soeters R

The FIGO classification of endometrial cancer necessitates the accurate assessment of myometrial involvement to determine the extent of primary surgery required. If > 50 % of the myometrial thickness is infiltrated by the endometrial cancer then

pelvic lymphadenectomy is required in addition to the standard surgery of TAH/BSO. This surgery also necessitates the expertise of a gynaecological oncologist.

Studies have shown that 3 dimensional ultrasound is as effective and has cost advantages over the other methods of detection (pelvic MRI and frozen section.)

I will present the ongoing data of a small pilot study of those patients with endometrial cancer who undergo transvaginal 3D ultrasound and pelvic MRI (prior to hysterectomies) and then frozen section at the time of their surgery (operators blinded from each other's findings). The accuracy and limitations of the techniques as well as cost analysis will be reported.

13. Detecting early-stage epithelial ovarian cancer during surgery, in theatre, in five minutes

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Objectives: Early-stage epithelial ovarian cancer is missed in 2-14% of cases during ovarian cyst surgery, when no frozen section is performed. Frozen section is not always available at the hospitals where this surgery is performed by gynaecologists, and even at many academic medical centres, frozen section is not available at all times of the day/during the weekends. It has been shown clearly that the first surgery for ovarian cancer is the most important one, and if done in the correct way, will improve patient prognosis. Ovarian cancer surgery should be performed by a gynaecologic oncologist, or one in attendance. We had hypothesized that there would be a biomarker within ovarian cyst fluid that would be able to distinguish cancer from non-cancer, in both early-stage and late-stage disease.

Design and method: We collected ovarian cyst fluid samples during surgery from 168 patients with epithelial ovarian tumour from the Department of Obstetrics & Gynaecology, National University Hospital in Singapore and also from six hospitals in the Southeast Asia region from 2004-2009. We measured haptoglobin concentration in cyst fluid using both in-house sandwich enzyme-linked immunosorbent assay (ELISA) and a rapid colorimetric assay which quantifies haptoglobin in five minutes. We compared the test accuracy among ELISA, rapid assay and intra-operative frozen section in discriminating between benign ovarian tumours and ovarian cancers.

Results and conclusion: Haptoglobin measured by ELISA was excellent in identifying early stage cancer. Development of a rapid test using a dye-binding assay

allows the test to be performed in the operating room, giving the surgeon a new method of making rapid surgical decisions about further management. This is the first study where an intra-operative tumour marker has been utilised in the differentiation between benign and malignant ovarian lesions.

14. Minimally invasive surgery for endometrial cancer

Soliman PT

MD Anderson Centre, Houston, Texas, USA

The role of minimally invasive surgery for the treatment of endometrial cancer has continued to increase over the last decade and many would consider it part of standard of care treatment for this disease. The objective of this presentation is to review the current published studies on minimally invasive surgery for the staging of endometrial cancer. This will also include information on surgical techniques, different minimally invasive approaches, complication rates, outcomes, and quality of life.

15. The relationship between endometriosis and endometrial cancer

Dreyer G

University of Pretoria

Endometriosis occurs by definition outside the endometrium, while endometrial cancer occurs by definition in the endometrium and uterine lumen. Endometrial cancer cannot, therefore develop from endometriotic implants. Various extra-uterine malignancies have been described to develop from endometriotic implants, mostly then with some features of endometrioid histology.

Endometriosis and endometrial cancer do share many characteristics, though, and these will be explored. The two conditions are both overgrowth diseases which can be classified as neoplastic, both originate from the endometrial cells and both diseases are usually but differentially hormone sensitive. The conditions are both probably monoclonal in most cases and contain important mutations that regulate cellular growth rate and the escape from normal growth control. More mutations will regulate implantation and dissemination or metastatic ability.

The embryological origin of the uterus is the Mullerian tube, consisting of multipotential stem cells which will develop into the tubular structures of the female internal genitalia. It is postulated that just underneath the basal layer of the endometrium a layer of cells remain that could retain some stem cell characteristics. These cells are dubbed the archimetra, or ancient

uterus. From these cells the myometrium will develop, consisting of miometrial cells which have both muscle structures and stroma cells. The endometrial basal layer also originates from the archimetra, and endometrial cells develop both stromal and glandular cells.

It is clear that endometriotic cells have a different potential for implantation and growth than normal shed endometrium. It also appears that these implants originate from a single clone and this implies that the glands and stromal elements in endometriosis originated from a multipotential cell which differentiated into both parts after implantation. This is the origin of the theory that postulates that endometriosis originates from endometrial basal layer cells or even from archimetral cells. Interestingly all these factors and monoclonal growth and dedifferentiation also apply to endometrial carcinoma.

Hormonal receptors originate from the stem cell that gives rise to the neoplasm and interestingly also responds to environmental factors. Both conditions are very responsive to hormonal manipulation and have been shown to express hormone receptors.

The intact basal membrane in the endometrium prevents invasion of cells into the myometrium thus

prevents adenomiosis and also should prevent placenta accreta. In the peritoneum, this will prevent invasive growth of endometriosis and in the uterus miometrial invasion of endometrial cancer. Obviously invasive behaviour is a result of the interaction between an (intact) basal membrane and the characteristics of the malignant cell.

Molecular and genetic factors are unravelled that are shared between these diseases and these will be shortly discussed as will the epidemiological risk factors shared between these diseases.

16. Minimally invasive surgery for cervical cancer

Soliman PT

MD Anderson Centre, Houston, Texas, USA

The role of minimally invasive surgery for the treatment of early cervical cancer has continued to increase over the last decade. The objective of this presentation is to review the data available supporting the feasibility of both laparoscopy and robotic surgery for the treatment of early cervical cancer. In addition, we will discuss current studies on the use of laparoscopy for the surgical staging of more advanced cervical cancers.