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Gynaecological Malignancies

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From the President's Pen

Greetings from AOGD

Wishing each and every member of AOGD a very happy and prosperous new year 2021. I hope this year brings lots of happiness, good health and bright hopes to all the members of AOGD. Wishing the corona crisis to die its natural death and we all thrive in perfectly healthy environment in the new year.

The New Year 2021 will also help us to spring back to our normal lifestyle. We are hoping this year to be for exciting, healthier, successful and full of growth. We will hopefully have physical meetings and will be able to meet our friends and colleagues. Though we also enjoyed the virtual meetings and continued with our learning and academic growth. May be in future we may have mixture of both i.e. hybrid meetings with physical and virtual components added. "Change is inevitable". So we also keep changing and innovating for better academics and brighter future.

This bulletin is on oncology and we have the privilege of having stalwarts in oncology writing important topics. We have inputs from Dr. Sarita Shamsunder, Dr. Sumita Mehta, Dr. Rupinder Sekhon, Dr. Shalini Rajaram, Dr. Seema Singhal, Dr. Rama Joshi, Dr. Harsha Khullar and Dr. Dinesh Kansal.

The month of January 2021 is also a month for Cervical Cancer Prevention. AOGD is planning activities for that event.

Wish you all again happy new year, brighter and healthier days ahead.

Long Live AOGD!

Dr Mala Srivastava
President, AOGD

From the Vice President's Pen

Greetings to all members of the association!

Hope you and your families are safe and doing well !

While we are in this most unprecedented time of uncertainty, volatility, and adversity, I wish you all a hope-filled and courageous heart!

As we enter into **year 2021 of the 21st century** and the **last quarter of our tenure as the secretariat of AOGD**, we are hopeful that soon there would be restoration of life towards normalcy.

This Pandemic has taught us a lot of new things. There has been a **Paradigm shift in our approach to Teaching and Learning**; from live class-rooms to virtual Webinars, live OTs to Electronic relays, Live Conferences, Workshops, Quizes and Competitions to all E- Conferences etc and so on and so forth.

Through AOGD initiatives, we have always strived to ensure our best efforts to impart knowledge so as to be able to elevate the level of care in women's health and ensuring that all women have equal opportunities to a healthy life.

Our Editorial Board's efforts in that direction, have beautifully shaped this month's **Bulletin on Gynae Oncology**. I'm sure we'll all learn a lot from the experts.

As has been said - **"Never lose Hope. Storms make people Stronger and never last forever"**- Roy T Bennette

Wishing a very 'Happy and Healthy New Year' , Lohri and Republic Day to everyone!

Regards,

Dr Kanika Jain
Vice President, AOGD

From the Secretary's Desk

Greetings to all !

As 2020 has been a year of unexpected superlatives courtesy of the pandemic, I wish that year 2021 will prove to be healthier, happier and CORONA free.

The academic activities in the month of December-January continued to be on the virtual platform as webinars and e-CMEs.

Our editorial team has brought the AOGD E-bulletin January version dedicated to **Gynae Oncology**, which should be of great interest and immense use to our readers.

Looking forward to your continued support.

The magic in new beginnings is truly the most powerful of them all- JOSIYAH MARTIN

Warm Regards

Dr Mamta Dagar
Hon. Secretary

Monthly Clinical Meeting

AOGD Monthly Virtual Clinical Meet will be organised by Ram Manohar Lohia Hospital, New Delhi on 29th January, 2021 from 04:00pm to 05:00pm.

From the Guest Editor's Desk

Dr Harsha Khullar
Guest Editor

Dr Geeta Mediratta
Chief Editor

Dr Chandra Mansukhani
Co-Editor

Dear Friends,

A very happy healthy and safe new year to all of you from secretariat of AOGD!!!

As you all know that the result of any intervention is determined by its impact on quantity and quality of life which is measured against the maternal and psycological costs. Most people will find out about their illness too late for curative medical treatment. Gynaecologic oncologist is in a unique position to function collectively as a primary care provider allowing comprehensive transfer of treatment with an emphasis on patients quality of life.

World health assembly recognises cancer cervix as a public health problem and WHO has developed guidelines on control and prevention of cancer cervix by vaccination and screening. Dr. Saritha Shamsunder has described about the "**Emerging role of STIs in CIN and cervical cancer**" and "**HPV vaccination**" has been dealt in detail by Dr. Mala Srivastava.

The cornerstone of managing endometrial cancer is surgery and there is a paradigm shift to minimal access surgery. Dr. Rama Joshi has discussed about the innovative method "**Robotic platform as a technology advances**" and Dr. Dinesh Kansal has given in depth description of the "**Sentinel lymph node biopsy in carcinoma endometrium**". The role of minimally Invasive technique in vulval cancer is also coming up because of low post operative complications and is discussed in detail in the topic of "**Role of Minimally Invasive technique of vulval cancer**" by Dr. Swati Tomar.

"**Smooth muscle tumour of uncertain malignant potential**" baffles the Pathologist and Oncologist with the diagnosis & management. Dr. Sumita Mehta has nicely dealt with this rare phenomenon. Similarly "**High grade serous carcinoma ovary**", Its diagnosis and management has been described in detail by Dr. Rupinder Sekhon.

The subject of controversy "**Breast cancer in pregnancy**" details about the diagnosis and management by surgery, chemotherapy and when to deliver the baby. It has been written and explained in detail by Dr. Shalini Rajaram along with Dr. Rahul Modi and Dr. Bina Ravi.

The budding Gynaecologist Dr. Huma Ali has worked on "**Contrast enhanced ultrasound in Gyanecological practice**". She has tried to discuss every point regarding the medium used and how to differentiate between benign and malignant uterine neoplasms.

I extend my sincere gratitude to all the contributors for this Gynaecological Oncology Bulletin of AOGD. I hope all of you enjoy reading various topics which we tried to include in this.

Stay safe & stay healthy.

We welcome any suggestions from esteemed members.

Happy reading!

Dr Harsha Khullar
Vice-Chairperson & Senior Consultant
Institute of Obst & Gynae
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Emerging Role of STIs in CIN and Cervical Cancer

Saritha Shamsunder
MD, FRCOG, FICOG, BSCCP, Accredited Colposcopist, VMMC & Safdarjung Hospital, New Delhi

Introduction

Cervical cancer is the fourth most common cancer in females in India in 2018. It accounts for 6.6% of all cancer in women and for 7.5% of all deaths per year[1]. Highest is 23.07/100,000 in Mizoram state and lowest is 4.91/100,000 women in Dibrugarh district in India. The high mortality rate from cervical cancer can be reduced through a comprehensive approach that includes prevention, early diagnosis, effective screening and treatment programmes.

Etiology & Risk Factors

For cervical cancer, human papilloma virus (HPV) is now considered the primary etiological agent. Nevertheless, HPV infection is often intermittent, and ultimately only a small number of women with chronic infection develop cervical cancer. Therefore, other cofactors may be involved in enhancing cervical cancer vulnerability following HPV infection by promoting persistence of HPVs.[2] Behavioural and lifestyle variables, as well as sexually transmitted infections such as bacterial vaginosis, Chlamydia trachomatis (C. trachomatis), herpes simplex virus, and human immunodeficiency virus were identified as potential cofactors involved in cervical cancer.

Cervical cancer risk factors include long-term use of oral contraceptives, high parity, cigarette smoking, human immunodeficiency virus co-infection, and sexually transmitted infections (STIs), such as Chlamydia trachomatis, Neisseria gonorrhoeae, herpes simplex virus type 2, Trichomonas vaginalis, Mycoplasma, Ureaplasma organisms. There is currently no definitive consensus on the effect of non-HPV STIs on an abnormal cervical cytology. HIV-diagnosed women have more frequent HPV infections, are more likely to become infected with several forms of HPV, and are more likely to have high-grade cervical disease compared to HIV-negative women. Early in 1993, cervical cancer was one of three AIDS-defining cancers by the AIDS-defining disease control centres. The World Health Organization classified cervical cancer as stage 4 AIDS defining illness in 2005.

Normal Cervicovaginal Flora & Bacterial Vaginosis

The primary colonizing bacteria of a healthy individual are of the genus Lactobacillus. Other bacterial species are frequently found in the vagina, such as the Gram positive cocci: *Atopobium vaginae*, *Peptostreptococcus* spp., *Staphylococcus* spp., *Streptococcus* spp., and *Bacteroides* spp., *Fusobacterium* spp., *Gardnerella vaginalis*, *Mobiluncus*, *Prevotella* spp., and Gram-negative enteric organisms, such as *Escherichia coli*. Mycoplasma and Ureaplasma are frequently found in the vagina. Bacterial vaginosis refers to a remarkable change in the vaginal microbiota to a dysbiotic environment, characterized by microorganism diversity and increased aerotolerant and strict anaerobic loads, including Gardnerella vaginalis, Mobiluncus and Aptopobium vaginae, and other fastidious bacteria, such as Megasphaera, Sneathia, and Clostridiales spp. Previous research showed that bacterial vaginosis is associated not only with reproductive and obstetric sequelae but also with precancerous cervical lesions.[3] Nonetheless, further studies are required to test the relationship and aggregate the evidence.

Molecular Mechanisms Causing Cervical Cancer

High-risk and low-risk HPVs cause infection by acquiring access through micro-abrasion to the proliferating basal cells of the stratified epithelium. A crucial event in HPV-mediated carcinogenesis leading to aberrant proliferation and malignant development is the incorporation of HPV DNA into the host cell genome. Integration usually results in increased expression and stability of transcripts encoding the viral oncogenes E6 and E7, known to inactivate and/or accelerate the degradation of various cell proteins, including the protein retinoblastoma (E7) and p53 (E6). Mechanism of other STIs causing cervical cancer is either potentiating the effect of pre existing HPV infection or complimenting & facilitating the

usual pathway of HPV causing cancer. There are other mechanisms which are yet to be studied more about, causing cervical cancer by STI's organisms other than HPV. A possible mechanism is C. trachomatis infection triggers the production of supernumerary centrosomes and chromosome segregation defects, facilitates multipolar mitosis, actively promotes chromosome instability, causes multinucleation, and thereby leading to transformation and tumor development. Additionally, C. trachomatis disrupted N cadherin-dependent cell-cell junctions and caused the breakdown of the N-cadherin/b-catenin complex in primary cultures of human cervical epithelial cells and in HeLa cells. More recently, Discacciati et al found Matrix metalloproteinases-9 / Reversion-inducing Cysteine-rich protein with Kazal motifs (RECK) imbalance during cervical inflammation induced by C. trachomatis might play a role in cervical carcinogenesis. Infection with HPV is established as a major cause of cervical cancer. A large body of evidence suggests that C. trachomatis infection may increase the risk of HPV acquisition as well as HPV persistence. They have similar behavioural risk factors, such as younger age and higher numbers of sexual partners. Hence two infection can occur together. Studies showed that coinfection of HPV and C. trachomatis was related to a higher risk of uterine cervical cancer, further strengthening this relationship.[4] It may be due to two mechanisms. First, HPV infection in the basal keratinocytes of the mucosal epithelium requires the presence of microabrasions or altered epithelium. Chlamydial infection could possibly lead to epithelial disruption, thus, facilitating the entry of the virus. Second, chlamydial infection might also disturb the immune response necessary to clear the virus.

Similarly Bacterial Vaginosis & Neisseria gonorrhoeae infection are associated with cervical cytological abnormalities in general population as shown by many studies which exhibited increased risk of ASC-US and ASC-US cytology after adjustment for carcinogenic HPV-positive status, indicating that Neisseria gonorrhoeae or bacterial vaginosis may function as an independent risk factor for formation of atypical squamous cell.[3]

Role of Screening & Early Detection of STIs in Cervical Cancer

In developing countries such as India, cervical cancer is a public health concern, so much so that India alone accounts for one-quarter of the global burden of cervical cancer. This is one of the leading causes of death from cancer, accounting for 17 per cent of all deaths from cancer among women aged between 30 and 69. It is projected that about 1 in 53 Indian women would experience cervical cancer over their lifetime compared to 1 in 100 women in more developed regions of the world.[5]

In both resource-rich and developing countries, sexually transmitted infections (STIs) are a major public health concern. STIs are mostly asymptomatic, which can lead to complications such as upper genital tract infections, infertility, chronic pelvic pain, cervical cancer, and chronic infection with hepatitis viruses and HIV. The primary goal of screening for STIs is to recognize and treat infected individuals before symptoms occur and to locate, monitor and treat their sex partners to avoid transmission and reinfection. Many patients suffer from asymptomatic disease which increases the risk of complications and sustained community transmission. Screening is therefore an effective approach in recognizing and treating contaminated individuals, who would otherwise go undetected. The drawbacks of screening relate primarily to the expense of the tests, the infrastructure needed to administer them, and the psychological and relationship implications of false positive tests that occur, especially among populations with low prevalence. Chlamydia trachomatis and Neisseria gonorrhoeae infections are extremely common and since the prevalence of these infections among adolescents and young adults is highest, the screening should focus these age groups. As same goes for the screening of cervical cancer, young age of onset of sexual activity leading to increased risk of contracting an STI.

Conclusion

Carcinoma cervix is the most common malignancy in females after breast carcinoma and as concluded by many studies, STIs enhance the risk of cervical carcinoma. Screening and early detection of sexually transmitted infections in the target age

population can definitely reduce the incidence of cervical cancer and contributing in decreasing the burden of disease. Therefore combined screening strategy should be followed that is screening of cervical cancer in patients with STIs and vice versa.

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HPV Vaccination- A road ahead

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The cancer cervix is among the fourth most frequent cancer in women all over the world. There were 570,000 new cases of cervical cancer reported in 2018.[1] The cancer cervix causes 7.5% of all deaths due to cancers of women. Out of which 85% of all deaths due to cancer cervix occur in low and middle income countries.

The World Health Assembly had adopted a global strategy to accelerate the elimination of cervical cancer by 2030. It recognizes cancer cervix as a public health problem. WHO also proposes goals and targets for the period 2020–2030(WHA 73.2)[2].

To eliminate cancer cervix these targets have been set to accelerate the process of elimination:

- The 90–70–90 targets are set which are supposed to be achieved by 2030 by the countries striving for cervical cancer elimination
- Approximately 90% of girls to be completely vaccinated with the HPV vaccine by the age of fifteen years.
- Approximately 70% of women to be screened by the age of 35years, and repeat screening by 45 years of age.
- Approximately 90% of women suffering from cancer cervix (both pre-invasive and invasive disease) to be identified and should receive appropriate treatment.
- As a result, a target of 4 per 100,000 women-year for cancer cervix can be achieved as a part of CA Cx elimination goal.

There is development of guidelines by WHO on control and prevention of cancer cervix by vaccination, screening and management of invasive cancer.

The infection with high-risk human papillomavirus causes cancer cervix. It is known that genotypes 16 and 18 of HPV, cause nearly 70% of cancer cervix all over the world.[3]

The infection with HPV is very common. More than 120 types of HPV are known, out of which at least 14 are responsible for causing cancer and are known as high risk type of HPV infection.

Most of the HPV infections will be cured spontaneously, yet persistent infection or re-infection with some high risk strains may cause pre-invasive or invasive cancers

- Cervical, vaginal and vulval cancer in women
- Penile cancer in men
- Anal cancer and cancer of oral cavity and throat in both men and women

Some of the HPV also causes genital warts. The viruses that cause genital warts are different from those that cause cancers.

The infection with HPV is considered sexually transmitted. Most of the infections usually occur after sexual debut. The younger women are more commonly infected with HPV infections, and mostly they also clear the infection within one or two years. But persistent infections or re-infection with HPV genotypes 16 and 18 may cause pre-invasive or invasive lesions of cervix.

As a result, among women never infected with HPV, the vaccination causes prevention of cancer cervix in almost 100% of cases.

At present there are three types of HPV vaccines that have been approved for protection against both HPV 16 and 18, known to cause approximately 70% of cases of cancer cervix. The Nona-valent vaccine, the third variety also protects against another five high risk HPV types that causes further 20% of cancer cervix. The vaccines which are providing protection against HPV 16 and 18 also have cross-protection against other less common high risk HPV types. WHO considers all the three vaccines equally protective against the cancer cervix. The two vaccines containing HPV 6 and 11 also protects against anogenital warts.[4]

Most of the HPV infections will clear spontaneously, but there is a risk that this HPV infection may become chronic and may lead to pre-cancerous or cancerous lesion of cervix. In women with normal immune system it may take 15 to 20 years to develop cancer cervix in case the infection with high risk HPV infection is persistent. But in women

with immune- compromise e.g. women with untreated HIV infection, it may take only 5 to 10 years to develop the cancer.[5]

The following are the risk factors for persistence of HPV infection and formation of cervical cancer:

- Infection with high risk HPV type.
- Immune-compromised women e.g. those with HIV infection
- Those with other STDs e.g. herpes simplex, chlamydia and gonorrhoea
- High parity
- Young age at sexual debut
- Young age at first birth
- Smoking and tobacco abuse

HPV vaccination is for girls of age 9 to 14 years. The girls who start the vaccination between age of 9 to 14 years need only two doses given at an interval of 6 months. The girls who start the vaccination after the age of 15 years need three doses of the vaccine. The girls who are immune-compromised e.g. those with HIV infection will also need three doses.

The schedule for three doses include second dose to be given two months after first dose, and the third dose to be given at least four months after the second dose. As a result, six months completes the vaccination schedule for the three doses.

Best is to give the vaccination before sexual debut. But in case, the women are already exposed and is sexually active, yet the vaccine will protect against the strains to which they have not been exposed and is contained in the vaccine. Of course, the vaccine will not protect against strains of HPV to which the women is already infected and exposed.

The reason why HPV vaccines are given between 9 to 14 years is the development of a better immunogenicity in younger teens. So that they are protected when they become sexually active. Most of the women catch HPV infections within 2 to 5 years of becoming sexually active. That is why it is important to vaccinate them before their sexual debut. Besides, anyone engaging in activities involving oral or genital contact can also acquire infection. The sexual intercourse is not essential to catch the infection.

It is important to remember that the HPV vaccine do not treat HPV infections.

About three HPV vaccines are available which are approved by the FDA and recommended by CDC.

These includes:

- Bivalent vaccine can be given to women upto 45 years of age
- Quadrivalent vaccine can be given upto 45 years of age
- The third one is nonavalent vaccine again made by Merck.

These HPV Vaccines are different

- Quadrivalent vaccine has capacity to protect against HPV 16 and 18 together with HPV types 6 and 11, these HPV infections causes genital warts in both women and men.
- It is licensed for use in men/ boys.
- These vaccines have different adjuvants and so they have different responses on body immunity.

FDA has approved all the vaccines as safe and effective. These vaccines have been tested in thousands of women all over the world. All the studies concluded no serious side effects.[6]

The common side effects include:

- Pain over the injection site
- Fever
- Dizziness
- Nausea
- Fainting attacks

Sitting or lying down for 15 minutes after the vaccination is a good precaution to prevent or to monitor these minor side effects. HPV vaccinations will not treat or remove any pre-existing HPV infections. It will also not cure conditions like warts or cancer.

This vaccine is not recommended during pregnancy. The studies have shown that none of the vaccines caused any problems for the babies whose mothers got the vaccine during their pregnancies. In case a woman gets the first dose of the vaccine and then gets pregnant, then she should postpone rest of the doses till after delivery. In case a woman gets the first dose of the vaccine and then gets pregnant, there is no reason to get a MTP done. This vaccination is safe during lactation. Women can be given this vaccine in the post-partum period.

Women vaccinated with HPV vaccine still needs to

be screened for cancer cervix by Pap's smear or by LBC or by primary HPV-DNA testing periodically as per the local guidelines.

Conclusion

The cervical cancer is a preventable disease. It is a cancer caused by HPV virus in most of the occasions. It can be prevented by primary prevention by vaccination which is readily available. The nonavalent HPV vaccine is thought to prevent more cases of cervical cancer, than the bivalent vaccine or quadrivalent vaccine. But these both vaccines have proven to be of good efficacy so far and have stood the test of time. WHO motto of elimination of cervical cancer can be achieved by 2030 by vaccinating 90% of girls. It is an achievable goal.

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Minimally Invasive Surgery in Endometrial Cancer

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Carcinoma endometrium is the most common gynecological cancer in developed countries with an age standardized incidence rate (world) of 8.4 per 100,000 women.[1] In developing countries, cervical cancer still remains the leading gynecological cancer but recently there has been an increase in the incidence of endometrial cancer. In India, the total number of estimated new cases of endometrial cancer in 2018 is 13,328 with an estimated 5010 deaths. The age standardized incidence rate (ASIR) of endometrial cancer in India is 2.3/100,000 women.[2] The rise in endometrial cancer in India is mainly attributed to changing trends in the lifestyle and reproductive profile of women, especially in urban areas. The majority of cases present in the 6th and 7th decades of life, with the mean age being 60 years at the time of diagnosis. Although it is conventionally thought to be a cancer of the postmenopausal period, 14% of cases are diagnosed in premenopausal women, 5% of whom are younger than 40 years.[3]

The main risk factor is exposure to endogenous and exogenous oestrogens associated with obesity, diabetes, early age at menarche, nulliparity, late-onset menopause, older age (≥55 years), and use of tamoxifen.[4-9] The relation between diabetes and endometrial cancer is controversial. Of the four cohort studies in which adjustments were made for body-mass index (BMI), an independent association between endometrial cancer and diabetes was noted in only one.[10-13] About 3% of endometrial cancers occur in women who have an autosomal dominant hereditary predisposition to cancer known as Lynch syndrome. The Society of Gynecologic Oncology released a clinical practice statement recommending systematic screening for Lynch syndrome in all women with newly diagnosed endometrial cancer. Colon and endometrial cancers are the most common malignancies in Lynch syndrome and occur at about equal frequency (range, 40%-60%).[14]

Surgery

Surgery is the cornerstone of management in endometrial cancer. The surgery of total abdominal hysterectomy, bilateral salpingo-oophorectomy in uterus confined disease and traditionally staging includes exploratory laparotomy through a midline vertical incision, exploration of pelvic and abdominal peritoneal surfaces, peritoneal washing with or without pelvic and para-aortic lymphadenectomy and depending on histology, omentectomy and excision of any abnormal area. Accurate surgical staging is the first step toward making adjuvant treatment recommendations.[15]

The reported five- year survival in endometrial cancer is encouraging and approaches 90% in stage I. The focus in the management is shifting to improve the quality of life of these long survivors. There is paradigm shift to minimal access surgeries to decrease the surgery related morbidities as majority of these patients are obese and have other comorbid conditions of mainly diabetes & hypertension. The trend of the surgery is changing to optimise the management approaches that limit extensive surgical staging using targeted approach of the sentinel node and will become increasingly important. With these modifications the issues of survival need to be addressed with the morbidity of the surgical approaches.

Given the substantial increase in the incidence of endometrial cancer, close association with obesity, and the increased prevalence among postmenopausal women, the Gynecologic Oncology Group LAP2 trial established the oncologic safety of minimally invasive surgery for the treatment of endometrial cancer. This study also demonstrated a reduction in postoperative adverse events and improved quality of life with a minimally invasive approach. The GOG demonstrated non inferiority of laparoscopy compared with laparotomy in the landmark randomized LAP2 trial. Patients were randomized 2:1 to laparoscopic versus open hysterectomy, BSO, and pelvic and para-aortic lymphadenectomy. Conversion to open surgery occurred in 25.8% of patients, with the most common reason being poor visualization, although this trial was done as minimally invasive surgery

was just gaining popularity, and surgeons were likely still in the learning curve. Operative time was longer for laparoscopy (204 vs 130 minutes), although intraoperative complications were similar, and fewer moderate-to-severe postoperative adverse events were seen in the laparoscopy group (14% vs 21%; P < .0001). Patients undergoing laparoscopy were slightly less likely to have a para-aortic lymphadenectomy performed (6.8%vs 3.2%; P = .0002). Full staging with pelvic and para aortic lymphadenectomy was done in 95.8% of patients undergoing open surgery and 91.5% of patients undergoing laparoscopy. The median node count was excellent and was similar between the 2 groups (17-18 pelvic nodes, 7para-aortic nodes), and 9% of both groups had lymph node metastases identified, suggesting similar efficacy in staging when done. Quality of life was better in the laparoscopy group at 6 weeks, although it was not statistically different between the 2 groups at 6 months other than in the domain of body image. The 3-year recurrence rate was 11.2% in the TLH group versus 10.2% with laparotomy. Five-year OS was not different between the 2 groups, although the study fell just short of meeting the non inferiority endpoint for recurrence-free survival (HR, 1.14 for laparoscopy; 90%to 95% CI, −1.28 to 4.0).[16]

The LAP2 results culminated in the American College of Obstetricians and Gynecologists (ACOG) and Society of Gynecologic Oncology (SGO) practice bulletin stating that minimally invasive surgery should be embraced as the standard surgical approach for comprehensive surgical staging in women with endometrial cancer. Minimally invasive surgery is especially important for obese patients, as obesity has been independently associated with increased surgical complications, and surgical morbidity is most profound in open surgery. In the LAP2 study, there was a direct relationship between patient body mass index and conversion from laparoscopic approach to laparotomy. In part, this was due to the protocol mandate that all patients have pelvic and para-aortic lymph node sampling performed.

The Laparoscopic Approach to Cancer of the Endometrium (LACE) trial evaluated outcomes and quality of life in 332 patients who underwent laparoscopic (TLH) versus open (TAH) hysterectomy for stage I endometrial cancer. Quality of life was improved across all domains except for emotional and social well-being for up to 6 months after surgery, which was the last time point evaluated.[17] Although operating time was longer for TLH compared with TAH (138 vs 109 minutes; P = .001), intraoperative complications were similar, and postoperative grade 3 and 4 adverse events were more likely in the TAH group (23.2% vs 11.6%; P = .004). DFS was similar between the 2 groups.[18]

A 2012 Cochrane Database systematic review evaluated 8 trials that included 3644 women undergoing laparoscopic versus open hysterectomy for endometrial cancer. No significant difference was seen in the risk of death or recurrence. Blood loss was lower in patients undergoing laparoscopy in an evaluable subset of patients with this variable reported, and severe postoperative adverse events were also lower in the minimally invasive group.[19]

In 1988, FIGO modified its staging system to emphasize thorough surgical / pathologic assessment of data, such as histologic grade, myometrial invasion, and the extent and location of extra uterine spread including retroperitoneal lymph node metastases. FIGO updated and refined the surgical/ pathologic staging criteria for uterine neoplasms in 2009. Surgical staging with nodal assessment for apparent uterine-confined endometrial cancer is critical to accurately determine the initial FIGO stage. Lymph node dissection, pelvic and para-aortic node dissection forms the important part of surgical staging. Targeted approach to sentinel nodes seems promising in redefining the role of the retroperitoneal node dissection in all uterus confined endometrial cancers and have shown impact on reducing the lymphadenectomy related morbidity.[20]

SLN Mapping

Lymph node status is the most important predictor of survival and provides risk assessment that guides postoperative treatment planning. Lymphadenectomy has been associated with prolonged operating time, additional cost, and increased morbidity including lymphedema, lymphocysts, and neuralgia. The SLN is the first node to receive drainage from a primary tumor. This lymph node, therefore, is most likely to harbour cancer cells for those cancers that spread via the lymphatic system. SLN mapping and ultrastaging

of SLNs have been proposed as a surgical method to reduce the morbidity of surgical staging while maintaining the prognostic information of lymph node status assessment.

SLN Mapping Efficacy

The initial results for SLN mapping were promising, including the SENTI-ENDO trial, which found 100% negative predictive value and 100% sensitivity of SLN when considering the hemipelvis as the unit of analysis and 97% negative predictive value and 84% sensitivity when considering the patient as the unit of analysis. However, a meta-analysis of 26 studies found a detection rate of 78% and sensitivity of 93%. A more recent meta-analysis identified a higher pooled detection rate (81%) and sensitivity of 96% for detecting lymphatic metastases, rates that approach those observed in breast cancer and melanoma. The authors suggest that these improvements may reflect gynecologic surgeons' growing experience with SLN mapping and increased use of more innovative dye and detection techniques.[21]

Robotic Surgery for Endometrial Carcinoma

Minimally invasive technology of robotic surgery has been increasingly used in the surgical staging of early-stage endometrial carcinoma due to its potential advantages over laparotomy, especially for obese patients. Prospective cohort and retrospective studies suggest that robotic approaches perform similarly to laparoscopy and result in comparable or improved perioperative outcomes. Oncologic outcomes appear to be comparable to other surgical approaches, although longer-term outcomes are still being investigated. In heavier patients, robotic surgery may result in less frequent conversion to laparotomy when compared with laparoscopic approaches and also appears to be safe and feasible in patients at higher anaesthesiologic risk.[20] Many surgeons find the laparoscopic approach difficult for routine clinical use because of increased operating time and a protracted learning curve. Robotic surgery has significant technical advantages and some disadvantages compared to conventional laparoscopy: advantages include 3D visualization of the operative field, a better dexterity that mimics the freedom of human hand and wrist motion and altogether improved ergonomics for the surgeon. Disadvantages are mainly lack of tactile perception and increased cost. Costs for robotic equipment and maintenance remain high.

The bulk of retrospective case series and two meta analyses (eight and nine comparative studies, 1,591 and 1,640 total patients, respectively) indicate similarities with laparoscopy in most categories, except for reduced blood loss and fewer conversions to laparotomy in robotic surgeries.[22,23]

Robotic and traditional laparoscopic surgery have better outcomes than laparotomy in terms of blood loss, blood transfusions, peri and post-operative complications, wound infection, post-operative pain, shorter recovery time and decreased length of hospital stay. Pelvic and para-aortic lymph node counts, which are a measure of surgical quality, were similar for the three modalities.

Conclusion

There have been surgical technological advances in the field over last two decades. Not many Gynae oncologists opted for the laparoscopic approach but robotic surgical technology was adopted well by the majority of the Gynecologic oncologists changing around 80% of the practice. RCT based evidence indicates that laparoscopic staging is similar to laparotomy with regard to surgical completion, adequacy of staging and cytoreduction, survival and recurrence rates. Yet, patients undergoing laparoscopic staging or laparoscopic hysterectomies still comprise only a small percentage of all hysterectomies in the US and around the world. Robotic platform overcomes some of the limitations of standard laparoscopic instrumentation and has increased the accessibility of gynecologic oncologists to minimally invasive techniques. Based on retrospective reports, robotic surgery for endometrial carcinoma is at the least non-inferior to laparotomy and traditional laparoscopy with respect to adequacy of staging, post-operative complications and overall and recurrence free survival rates. Robotic surgery has the advantage of lower rate of conversion to laparotomy and lower blood loss. Thus, minimally invasive approach should be considered to be the surgical treatment option of choice in endometrial carcinoma patients.

Minimally invasive surgical techniques continue to evolve as the next generation of robotic platforms which integrate tactile feedback and single-port laparoscopic and robotic instruments are being tested. The goal of all gynecologic cancer surgeons should be to perform surgery in a way that minimizes disfigurement and psychological trauma and preserves function. Innovative methods and instruments, such as the robotic platform, sentinel lymph node biopsy and single-port surgery continue to evolve as technology advances.

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Sentinel Lymph Node Biopsy in Endometrial Cancer

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Background

Endometrial cancer (EC) is one of the common gynecological cancers in the world. It is rising in incidence and mortality significantly. Lymph node evaluation is the key point in EC staging and prognosis. Sentinel lymph node biopsy (SLNB) involves removing a sentinel or watchman lymph node that is the first node involved in the movement of a tumour from the primary cancer to the lymph nodes. Since the flow of lymph is unidirectional, the spread of cancer usually follows an orderly progression, spreading first to regional lymph nodes, then the next echelon group of lymph nodes. The pathological status of SLN reflects the overall status of entire lymphatic basin. If this is negative, it is surmised that the other nodes are not involved. It is likely that sentinel nodal status could influence the administration of adjuvant therapies such as chemotherapy/ radiation or both. Among the gynaecological cancers, SLNB could perhaps make a significant impact in women with endometrial cancer. Moreover, sentinel node biopsy is performed in many women with breast cancer and is also becoming the standard procedure for women with vulval cancer.

Although lymphadenectomy is commonly performed as part of the surgical treatment of EC, the randomized trials have failed to show a survival benefit for lymphadenectomy. The Medical Research Council of ASTEC trial concluded that there was no benefit of systematic lymphadenectomy for early-stage EC on patients' survival or prevention of recurrence. These studies also demonstrated that lymphadenectomy was associated with an increased risk of complications and called into question the value of the procedure.

Endometrial Cancer

The cornerstone of treatment in most women with endometrial cancer is surgery involving a total hysterectomy and bilateral salpingoophorectomy with or without lymph node dissection. The lymph node metastasis is one of the most important prognostic factors in endometrial cancer. Some centres do not perform any form of node dissection, while others will perform a node dissection in aggressive endometrial cancers, such as serous cancer or grade 3 endometrioid cancer of the uterus. It is important to differentiate lymph node sampling from a systematic dissection. Lymph node sampling involves removing a limited number of nodes, often if these are suspected to be positive for metastatic spread, normally based on palpation and visual assessment of nodal size. A systematic lymph node dissection involves removing all the nodes within a nodal drainage basin irrespective of their size. It is unlikely that a lymph node dissection removing micro-metastasis offers any therapeutic benefit but it may identify more aggressive cancers requiring further adjuvant treatment such as chemotherapy and/ or radiotherapy.

Paradigm Shift in Surgical Staging

SLNB provides a more sensitive method of assessing the spread of apparent early stage endometrial cancer than a lymph node dissection, thus enabling targeted adjuvant therapy. There is also evidence for higher detection of lymph node metastasis with SLNB compared with standard lymphadenectomy.

Lymph node dissection becomes difficult with increasing obesity and carries a risk of vascular or nerve injury. The risk of leg lymphoedema following a node dissection is under-reported, with rates varying between 15% and 38%. The debilitating effects of lower limb lymphoedema cannot, however, be overestimated since it has a marked effect on the quality of life of long-term survivors. Ma et al found that infected lymphocysts were seen more frequently in patients with combined PALND plus PLND along with higher number of resected pelvic lymph nodes. Replacement of a lymph node dissection by SLNB reduces both acute and chronic morbidity associated with a full node dissection.

Adjuvant Therapy

In early endometrial cancers, lymph node status provides guidance for adjuvant treatment. EBRT

reduces the risk of loco-regional recurrence but has no significant impact on cancer-related deaths or overall survival. It is associated with significant morbidity and a reduction in quality of life. The role of radiotherapy and chemotherapy has been investigated in two RCTs: GOG 258 and PORTEC 3. The benefit of adjuvant chemotherapy for women with positive lymph nodes is supported by a meta-analysis. When compared with post-operative radiotherapy, giving combination chemotherapy resulted in significant improvement in overall and progression-free survival.

Who Should Be Offered?

The majority of women with endometrial cancer will have grade 1 or 2 endometrioid type tumours. Risk of nodal involvement in this group of women is low. A historic case series, which included 180 women with grade 1 cancers, reported the incidence of pelvic node positivity as 0%, 3% and 11% in women with no, inner third and outer third myometrial invasion respectively. The risk of extrauterine spread also increased with tumour grade. The preoperative grade based on endometrial biopsy may not always reflect the final grade of the hysterectomy specimen, with between 15% and 27% of women being upgraded. The majority of cancer centres and units will not offer such women a lymph node dissection as there is a low risk of finding a positive node. Instead the administration of adjuvant treatment for apparent stage I disease is based on the woman's age, the presence of lymphovascular space involvement and the depth of myometrial invasion on the hysterectomy specimen. Unfortunately with complete omission of lymph nodal dissection, a number of women with positive lymph nodes may miss out on the benefits of the adjuvant treatment.

Site for Injection of Tracer

There are a variety of methods for injecting radioactive tracer or coloured dye. These include-

a. Cervical injection
b. Hysteroscopic injection and
c. Subserosal myometrial injection.

Cervical injection is not only the most convenient because of easy access to the cervix, but also gives highest yield of SLN detection. Tracer is injected at 3 and 9 O'clock positions in cervical fibromuscular tissue; 2 ml on each side before starting the surgery. It is similar to the technique used for cervical cancer SLNB. Some studies have reported cervical injection as a single site and others in conjunction with subserosal myometrial injection. The main concern with cervical injection only has been the potential to miss metastatic spread through the ovarian drainage route to the para-aortic region, leading to false-negative results. However, Abu-Rustum et al demonstrated that the addition of a fundal injection to the cervical injection did not appear to produce a higher detection rate. Rossi et al injected Indocyanine green (ICG) either into the cervix or the endometrium (through the hysteroscope) and concluded that cervical injection achieved a higher sentinel lymph node detection rate.

Injection into the cervical stroma just under the epithelium seems to be the most commonly used route. Cervical injection seems to yield detection rates between 80% and 100%. Multiple studies have used the hysteroscopic injection technique into the endometrium to identify the sentinel lymph node. It is suggested that by visualising the tumour, this technique reflects the true drainage of individual endometrial carcinoma patterns most accurately. The method is logistically the most complex. The detection rate does not appear to be superior to the other two methods and has been reported to be between 50% and 82%. Niikura et al compared hysteroscopic with cervical injection and found cervical injection to be superior for sentinel node detection. Subserosal myometrial injection is favoured by some investigators. This technique is thought to have better detection for both drainage - pelvic and paraortic pathways but requires intraoperative injection of the tracer into the uterine body, which makes the use of technetium-99m (99mTc) technically difficult. Preoperative injection of 99mTc under ultrasound guidance would make this approach uncomfortable for the patient and rather difficult to inject the posterior aspect of the uterine corpus. It seems that detection rate increases with the number of injections at different sites of the uterine corpus. Detection rates vary widely; in the range of 0–92%.

Detection Techniques

Sentinel node mapping involves injecting a tracer substance into the vicinity of the primary tumour, followed by detection of the tracer and the

removal of the sentinel lymph node for Immuno-histopathological analysis. A variety of substances have been used.

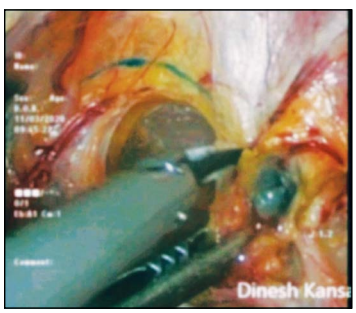
Broadly the tracer substances can be divided into-

1. Radio- active tracers
2. Blue dyes

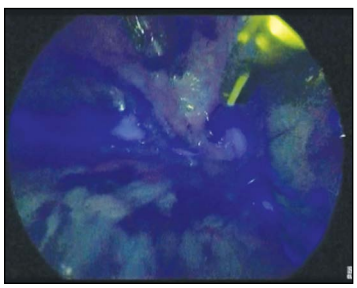
Technetium-99m Colloid

99mTc can be administered on the day before or on the same day as surgery. The injected substance is tagged with the radionuclide technetium-99m. Scintigraphic imaging is usually started within 5 minutes of injection and the node appears from 5 min to 1 hour. This allows for the preoperative detection of the sentinel node/s on each side with a single-photon emission computed tomography (SPECT) scan. This allows for accurate preoperative location of the node/s. Intra-operatively, the 99mTc is detected using a gamma probe.

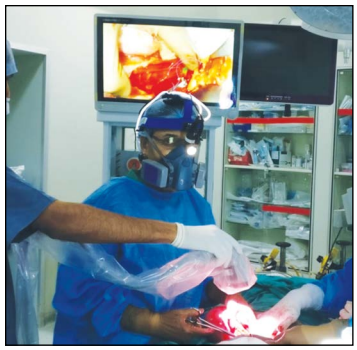
Many centres combine 99mTc with the use of a blue dye to provide a visual identification of the lymphatic channels leading to the sentinel nodes. About 15 minutes before the biopsy the physician injects a blue dye in cervical tissue in the same manner. Then, during the biopsy, the physician visually inspects the lymph nodes for staining and uses a gamma probe or a Geiger counter to assess which lymph nodes have taken up the radionuclide.



Methylene blue dye staining lymphatics leading to SLN on laparoscopy



ICG dye fluorescence with NIR imaging on laparoscopy



Tc33 fluorescence with hand held gamma camera

Indo- Cyanine Green Dye

Use of near infrared (NIR) imaging to detect a fluorescent dye such as ICG is a new technique with evidence to suggest it may be superior to blue dye alone. Technique is based on the ability of a specific dye or fluorophores, such as ICG, to fluoresce in the NIR light range. ICG is injected as 0.5% solution 2ml on each side in the cervix. The fluorescence occurs when a laser is emitted from an NIR imager which excites the dye; this produces a wavelength that is converted into a fluorescent image. The imager can be integrated into the laparoscope or robotic (firefly) system. Combining blue dye with a radio-tracer gives benefits of the blue dye technique (naked eye visibility) with nuclear medicine techniques (penetration of signal through intact tissue) in a single modality.

Blue Dye

A variety of blue dye substances are available including isosulfan blue 1%, methylene blue 1% and patent blue 2.5%. The blue dye is injected 10–20 minutes prior to the start of surgery, allowing time for the dye to enter the lymphatic channels and flow to the lymph nodes. Then, during the biopsy, the physician visually inspects the lymphatic channels leading to the sentinel lymph nodes for staining. Advantages of this method include the ease of use and the lack of need for specialist equipment. Disadvantages include the need to open the whole retroperitoneal space to visualise the nodes and the requirement for a degree of subjectivity with visual assessment.

Analysis of Sentinel Lymph Node

Standard histopathological assessment of lymph nodes will fail to detect micrometastases (0.2 mm

to 2mm). Hafner et al reported that using routine haemotoxylin and eosin (H&E) histology, the chance of identifying a cluster of less than three cell diameters (ITC) is only 1%. Sentinel lymph nodes are normally subjected to ultra-staging. This involves taking multiple thin sections from the single node combined with immunohistochemistry (IHC) for Cytokeratin 19. Frozen section of sentinel node is to be avoided as it would deteriorate the results of ultra-staging.

Ultra-staging is time consuming and expensive, making it unsuitable for larger numbers of nodes. The contribution of IHC is particularly relevant since between 18% and 20% of patients were upstaged after detection of micrometastases. In women with low risk endometrial cancer (grade 1 or 2 with less than 50% myometrial invasion), ultrastaging resulted in an almost 50% increase in the number of positive lymph nodes identified compared with standard lymphadenectomy techniques. In a large study of apparently early stage endometrial cancer, Holloway et al demonstrated that the sentinel lymph node mapped patients had twice as many lymph node metastases as the non-mapped group (30.3% versus 14.7%; $P < 0.001$). The relationships between micrometastases and risk of recurrence and prognosis have been demonstrated in an increasing number of malignancies including cancers of the breast, vulva, stomach, colon, prostate and melanoma. This suggests that micrometastases in lymph nodes are an indication for adjuvant therapy. Newer commercial automated nodal assessment technologies, including one step nucleic acid amplification, are emerging with a small study reporting a positive predictive value of 93.3% and sensitivity of 82.4% in endometrial cancer.

Reliability of Sentinel Lymph Node Biopsy

The reliability of SLNB is based on the detection rate of the sentinel node, the sensitivity of the procedure and the false-negative rate. Within the context of SLNB, it is almost impossible to find false positives and the specificity is therefore considered 100%. Because there are three potential nodal basins for lymphatic drainage in endometrial cancer; two pelvic and the para-aortic area, it is important to define how detection, sensitivity and false-negative rates are measured. The majority of studies report pelvic SLNB data based on the procedure performed: i.e. two sides of the pelvis counts as two procedures. Occasionally, a sentinel node will not be identified on one side of the pelvis; in this situation, a formal/complete lymph node dissection is commonly carried out on that side of the pelvis. Reasons for the failure to identify a node include problems with injection of the primary tumour site and blockage of lymphatic channels due to the tumour. The latter occurs especially with large primary tumours.

The Sentinel Node and Endometrial Cancer (SENTI-ENDO) study included 125 women with endometrial cancer treated in nine French cancer centres by cervical injection of 99mTc and patent blue dye. All the participating centres had previously performed at least 30 SLNBs in endometrial cancer and used ultrastaging of the SLNB. These results were compared in a meta-analysis of 26 studies published in 2011. In the SENTI-ENDO study the detection rate in the left and right hemipelvis was 77% and 76% respectively, with a detection rate per woman of 89%. Of note, 5% of woman had para-aortic sentinel lymph nodes, all of whom also had pelvic sentinel lymph nodes. This study was powered to consider each hemipelvis separately. Kang et al assessed studies using a variety of techniques and reported a detection rate of 78% per procedure on the hemipelvis, with the hysteroscopic route being associated with a lower detection rate than cervical injection.

Sensitivity

The sensitivity in the SENTI-ENDO study was 100% per procedure but 84% per woman. The meta-analysis by Kang et al reported a similar result, with 93% sensitivity per woman with the majority, but not all, of the studies using ultrastaging. This did not change when studies including more than 30 women only were used to calculate sensitivity. FIRES trial results showed Negative predictability in 99.6% and positive sentinel node detection in 97%; although 28% of the FIRES study population had high grade histologies, which are at highest risk for metastases and isolated para-aortic metastases.

False-negative Rate and Negative Predictive Value (NPV)

The false-negative rate represents the rate of technique failure and is especially important if

SLNB is used to determine whether adjuvant chemotherapy is given. In the SENTI-ENDO study, the false-negative rate was 0% and there was a negative predictive value (NPV) of 100% per procedure. Of note, three women had positive nodes (two pelvic and one para-aortic) and a negative pelvic SLNB on the contralateral side of the pelvis. In this context, the NPV was 97% per woman. In the Kang meta-analysis, the calculated false-negative rate was 1% based on a risk of positive nodes of 10%.

Distribution- Which Group of Nodes are Important

The lymphatic drainage of the uterus normally occurs through the parametrium to the pelvic sidewall including spread to the iliac and obturator nodes. Metastatic disease may then spread from the pelvic sidewall to the common iliac and then para-aortic nodes. The alternative drainage, including the uterine fundus, may also occur along the ovarian vessels directly to the higher para-aortic nodes. It therefore appears logical that fundal tumours may spread along the ovarian vessels directly to the aortic nodes above the inferior mesenteric artery at the level of the renal vein (especially on the left). This suggests that if the sentinel node was in the para-aortic region, it might be missed by techniques that involve injecting an agent into an area that drains to the pelvic nodes.

However, data from several studies examining individual endometrial cancers that had been completely staged with both pelvic and para-aortic node dissection, suggested that isolated metastases to the high para-aortic region were between 1% and 6%. Abu-Rustum et al reported a series of 42 patients surgically staged, which included all the tumour grades and histopathological types. Approximately 1% of women had isolated para-aortic nodal metastasis with negative pelvic nodes. A further study suggested that only 1.5% of women will have positive para-aortic nodes when the pelvic nodes are negative. Even in women deemed to be at high risk, a prospective study of 742 patients reported that only 3% had positive para-aortic nodes when the pelvic nodes were negative. Kumar S and Khoury-Collado F et al also had similar results in their studies.

Minimally Invasive Surgery

The minimal access surgery, robotic/ laparoscopic/ V-NOTES, is now the preferred approach for surgical staging of EC. It has been associated with reduced pain score, reduced hospitalisation, and earlier resumption of daily activities when compared with open surgery. Laparoscopic surgery is also preferred for sentinel node detection due to the increased magnification and illumination of the surgical field. Approximately 57% of the cases have significant obesity. They may be offered robotic surgery for the best outcome. Introduction of sentinel lymph node biopsy reduces operative times and improves peri-operative surgical outcomes of minimally invasive staging for apparent early-stage endometrial cancer with the morbidity as low as hysterectomy alone.

Advantages of SLNB Over Complete Lymphadenectomy

1. Surgery can usually be accomplished by minimally invasive route
2. Better yield for positive lymph node detection
3. Adjuvant treatment is offered to more patients with positive SLNB and unnecessary radiotherapy is avoided if SLNB shows absent metastasis
4. Reduced OR and anaesthesia time
5. Less lymphoedema and lymphoceles
6. Decrease in number of blood transfusions
7. Decreased incidence of blood vessel and nerve injury
8. Early resumption of work
9. SLNB is comparatively cost effective

Conclusion

Sentinel node detection in endometrial cancer is feasible and has reasonable test performance. It has been suggested that it may resolve the debate within the gynaecological cancer community on whether or not to carry out pelvic node dissection in early endometrial cancer. Current protocols for SLNB recommend that if a sentinel node on one side of pelvis is not identified then a full pelvic node dissection should be carried out on that side. This would be a significant change of practice for some, especially in low risk women. Alternatively, it could be argued that if a centre's current practice is not to perform a lymph node dissection then if no sentinel

lymph node is identified then a full dissection should be avoided pending further published data.

The sentinel lymph node status would replace or complement indications for adjuvant treatment based on uterine factors or a woman's age. It is likely that it would become an additional factor in a similar manner to breast cancer management. It is clear that low risk group of women with endometrial cancer would benefit most. At the same time, findings from Fires study indicate that SLNB may be beneficial in high risk group as well. Determining the risk of lymph nodal involvement preoperatively is difficult and lymph nodal involvement is one of the best prognostic factors and criteria for adjuvant treatment. With the low morbidity of the SLNB procedure, it might be desirable if all women could undergo SLNB to help in the selection of those who require chemotherapy or radiotherapy. The most frequent type of endometrial cancer is endometrioid carcinoma, which accounts for more than 80% of cases. This makes it the third most common cause of death in cancers which only affect women, behind ovarian and cervical cancer. To limit the potential short and long-term morbidity of lymphadenectomy, the use of SLNB procedure increased rapidly from 2011 onwards.

Sentinel lymph node mapping has the lowest costs and highest quality-adjusted survival. SLNB is the most cost-effective strategy in the management of low-risk ECs as per Update 2018. However, in near future, adjuvant systemic therapy for all stages may not be determined by histology, rather by molecular Bio markers e.g. p53, HER2, MSI.

Further Reading

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Smooth Muscle Uterine Tumor of Uncertain Malignant Potential: An enigma

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Introduction

Smooth Muscle Uterine Tumor of Uncertain Malignant Potential(STUMP) is used to define a group of rare heterogenous subtype of smooth muscle tumors of the uterus which are histologically and clinically distinct from the benign leiomyoma (LM) and malignant leiomyosarcoma (LMS). This tumor has continued to baffle pathologists and oncologists both, with its diagnosis and management. It is a rare slow growing tumor, with an incidence of 0.1% in histological specimens of women undergoing myomectomy or hysterectomy for a preoperative diagnosis of leiomyoma[1]. Very limited data is available in literature regarding its clinical management and follow up. In this article we wish to summarize the current knowledge and tackle the dilemmas regarding its diagnosis and management.

The Challenging Classification & Differential Diagnosis

The classification of uterine smooth muscle tumors is based on the assessment of three histopathologic characteristics: *degree of cytological atypia, presence of coagulative tumor cell necrosis (CTCN) and mitotic index* (number of mitotic figures / 10 high power fields).[2] Of these presence of CTCN is pathognomonic of STUMP diagnosis. CTCN shows presence of an abrupt transition between necrotic cells and preserved cells though outlines of the nuclei from the necrotic cells can often be seen and inflammatory cells are uncommon. On the other hand, hyalinizing necrosis which is commonly seen in leiomyomas, shows presence of a zone of hyalinized collagen interposed between the dead cells and the preserved cells, suggestive of an infarcted region being organized by granulation tissue.[3, 4] The correct diagnosis of STUMP tumors, however, can be challenging as many histologic characteristics overlap with rare subtypes of leiomyoma variants.

Kempson and Hendrickson originally gave diagnostic criteria for evaluation of smooth muscle tumors of the uterus and classified them as follows:[3]

Leiomyoma – absent cytological atypia, no tumor cell necrosis

Leiomyosarcoma - moderate to severe cellular atypia, > 10 mitosis/ 10 hpf, no tumor cell necrosis

Atypical Leiomyoma - moderate to severe cytological atypia, <10 mitosis/10 hpf, and no tumor cell necrosis.

If both moderate to severe atypia and tumor cell necrosis are present, the tumor is a leiomyosarcoma whatever the mitotic index.

The Stanford criteria[2] for the histologic diagnosis of STUMP is presence of any unusual combinations of the three features that do not satisfy the *current Stanford criteria for Leiomyosarcoma:*

- Diffuse moderate to severe atypia
- Mitotic count of at least 10 mitotic figures/10 hpf
- Tumor cell necrosis

Absence of necrosis and atypia and <4 mitosis indicate benign leiomyoma. Diagnosis of atypical leiomyoma is defined by multifocal moderate to severe atypia, a mitotic count of <1/10 hpf and no tumor cell necrosis.

Ip et al stressed on the importance of mitotic figures in differentiating LM from STUMP, especially LM with presence of bizarre nuclei, but the presence of pseudo – atypical mitosis with degenerating nuclei makes it difficult to distinguish from true mitosis.[5]

Bell et al subclassified STUMP under the following categories[2]:

- Smooth muscle with low malignant potential: Mitotic index < 10 mitotic figures / 10 hpf, coagulative necrosis is present and no atypia to mild atypia seen.
- Atypical leiomyoma but limited experience: Mitotic index<20 mitotic figures/10 hpf,

coagulative necrosis is absent, severe atypia is seen.

- Atypical leiomyoma with low risk of recurrence: Mitotic index <10 mitotic figures/10 hpf, coagulative necrosis is absent, moderate to severe atypia is present.

Guntupalli et al[6]defined STUMP in the presence of any one of following criteria:

- No atypia, presence of tumor necrosis, mitosis ≤ 10/10 hpf
- Presence of diffuse atypia, no tumor necrosis, mitosis ≤ 10/10hpf
- No atypia, no tumor necrosis, mitosis ≥ 20/10 hpf
- Cellularity or hypercellularity with mitosis ≥ 4/10 hpf
- Irregular margins or vascular invasion in peripheral side of tumor.

D' Angelo and Prat[7] described the following criteria for diagnosis of STUMP

- Tumor necrosis in typical leiomyoma
- Tumor necrosis and > 10 mitosis / 10 hpf
- Remarkably diffuse or focal atypia and borderline necrosis

Gupta et al in 2018[8] has suggested redefinition of STUMP and inclusion of following criteria to predict adverse outcomes:

- Tumor necrosis but difficult to define
- Diffuse or multifocal atypia and mitotic counts near threshold for malignancy
- More than 15 mitosis/10 hpf
- CTCN in multifocal or irregularly shaped foci
- Atypia or proliferative activity intermediate between benign and malignant
- Myometrial invasion without usual features of malignancy
- Atypical mitotic figures without canonical features of malignancy.

Various researchers, Deodhar et al, Xiropotamouet al, Amant et al, have emphasized that only coagulative necrosis is typical to diagnosis of STUMP. They also found coagulative necrosis as the most strongly associated factor with malignant behavior of STUMP.

WHO defines that a uterine smooth muscle tumor that cannot be unequivocally categorized as benign or malignant should be defined as STUMP[9].

Distinguishing Uterine Leiomyoma, STUMP and LMS Pre-operatively

Demographic Profile

The rarity of this tumor is a limitation for availability of adequate demographic data to find associations or risk factors for its occurrence. The largest retrospective analysis by Guntupalli et al[7] of 41 patients, was not able to demonstrate associations with any race or ethnic group. The tumor affects women in the perimenopausal age group with a mean of 45 years similar to LM and LMS. [5,6,10,11]

Symptoms

The clinical signs and symptoms mimic those of LM and LMS. These include presence of pelvic pain, abnormal uterine bleeding, pelvic mass, symptoms secondary to anemia or compression, or a combination of them[5,6,10]. Joseph et al reported pelvic mass as the most common presentation in 50% of the women, while menorrhagia was present in 16.7%. Juhaz Boss et al[11] in a review article on LMS suggested that if a woman less than 45 years has history of abnormal uterine bleeding, a fast growing tumor or a tumor more than 8 cm in diameter should have a careful evaluation by D&C or endometrial biopsy (EMB) to rule out STUMP.

Imaging Modalities

Ultrasonography: There are no specific ultrasound features to differentiate STUMP from benign leiomyoma. However, the presence of a vascular mass with irregular outline or anechoic necrotic areas in the tumor on ultrasound imaging may suggest aggressive nature of a sarcoma[12]. Bonneau et al reported sonographic presence of single tumor, absence of acoustic shadowing and presence of free fluid to be more commonly associated with STUMP/ malignant mesenchymal tumor. [13]

Magnetic Resonance Imaging: It is the most sensitive imaging modality available to preoperatively diagnose LMS. MRI has been used to differentiate benign leiomyomas and LMS utilizing increased signal intensity, but evidence is still lacking to distinguish STUMP from leiomyoma.

Typical features of uterine leiomyomas on MR are described as well demarcated hypointense masses on T2W1. Mitotic figures and cytological atypia which are features of STUMP and LMS cannot

be demonstrated on MR but high cellularity can be seen as hyperintense signal areas on T2W1.[14] Coagulative necrosis which is a distinct feature of STUMP, cannot be directly appreciated as hyperintense signal areas on T1W1[15]. If LMS or STUMP do not have any hemorrhage, then it is difficult to obtain a correct diagnosis.

Tanaka et al in their study to define MR findings of STUMP concluded that in the presence of more than 50% of the lesion showing signal T2W1, presence of any small area of high signal within tumor on T1W1 and presence of unenhanced pocket like areas after contrast administration, is highly suggestive and is enough reason for the surgeon to defer uterus preservation in such cases.[15]

Sato et al in a study to assess the clinical application of Diffusion weighted imaging (DWI) and Apparent diffusion co-efficient (ADC), to pre-operatively differentiate LM from LMS, found100% sensitivity and 94% specificity when the two were used together.[16] All low intensity lesions were suggestive of leiomyoma nodules while leiomyosarcoma presented as intermediate or high intensity areas in the uterine wall on DWI. ADC cut off value is $1x10^{-3}$ mm^2 and values more than or equal to this are associated with leiomyomas. Tumors with increased cell density like cellular leiomyomas and malignant tumors have high signal intensity (SI). ADC may help to differentiate benign from malignant smooth muscle tumors especially those with high SI.

Positron Emission Tomography (PET Scan) – It has a limited role in differential diagnosis as leiomyomas also take up FDG (fluorodeoxyglucose) on PET scan as a marker of cellular proliferation.

Role of Immunohistochemistry

Histologic distinction between malignant and benign smooth muscle tumors remains challenging, therefore researchers evaluated the role of immune-histochemical markers expression to aid diagnosis. There is no available data yet to formulate any recommendation using immunohistochemistry for diagnosis of STUMP. The most commonly studied markers are p16, p21, p53, Ki 67,Bcl-2, progesterone and estrogen receptors.

- p53 expression is significantly high in leiomyosarcomas but the frequency of p53 positivity ranges from 13% to 56.5% in various studies.
- Overexpression of p53 and high Ki 67 labeling index are found in leiomyosarcoma and can be used to distinguish it from benign leiomyoma or STUMP.
- Overexpression of p16 is seen in LMS and is higher than in leiomyomas. Chen et al found strong and intermediate to diffuse staining pattern for p16 in all 100% cases of leiomyosarcoma and STUMP as opposed to only 14% of leiomyomas in their study.
- Use of a higher threshold value for p16 staining improves the significant increase in expression from benign to leiomyosarcoma.
- PR expression is found to be present in 82- 100% leiomyomas, 75-90% in leiomyoma variants, and <25% of LMS. This delineates no difference in PR expression between leiomyomas and leiomyoma variants, but significant difference when comparing leiomyoma variants such as STUMP and leiomyosarcoma.
- Bcl-2 is expressed more frequently in leiomyomas as compared to STUMP or leiomyosarcoma. If Bcl-2 is expressed in STUMP or malignant tumors, it is indicative of a good prognostic factor.

The latest addition to this list is Caveolin-1 (Cav-1) and AT-rich interactive domain 1 alpha (ARID-1A) expression in uterine smooth muscle tissue. Cav-1 and ARID-1A are known as signal regulators and tumor suppressors and were used in the differential diagnosis of uterine Smooth Muscle Tumors (SMTs). Ayaz et al. reported that as the tumor becomes malignant, expression of perivascular Cav-1 increases significantly. Nuclear staining for ARID-1A in LMS was shown to be significantly higher than in STUMP and benign leiomyoma, making it another potential marker of malignancy.

The use of immunohistochemistry has a definite role in diagnosis and risk stratification of the tumors but its utility should be weighed against the cost of the tests.

Management: Myomectomy versus hysterectomy

Uncertain malignant potential, indolent behavior, and prolonged survival of the tumor, leaves the management at the crossroads for the patient as

well as the oncologist. Outcome of STUMP does not differ if the initial surgery was myomectomy or hysterectomy. *A post-operative diagnosis of STUMP on myomectomy specimen does not warrant a reoperation and hysterectomy.* Various retrospective analysis did not find any differences in long term outcomes of patients who had undergone myomectomy or hysterectomy.

Hysterectomy is currently considered the gold standard and it is especially recommended for women who have completed their childbearing. On the other hand, the choice between myomectomy and hysterectomy represents an extremely important issue in the management of STUMP in young women balancing the risk of recurrence and the preservation of fertility. It is important to discuss with the patients, regarding the histological features of the tumor, the psychological impact of hysterectomy in young women, the desire for fertility, pregnancy outcomes in the case of myomectomy and the chances of recurrence of the tumor either as STUMP or leiomyosarcoma, and the need for strict surveillance.

The following recommendations are suggested by the National Comprehensive Cancer Network Guidelines for STUMP:

- If a patient has been diagnosed with STUMP after tissue sample from biopsy, hysterectomy is recommended. This is regardless of the route of hysterectomy which can be abdominal, vaginal or laparoscopic.
- Patients with surgically removed STUMP lesions should have a baseline CT scan of the chest, abdomen and pelvis. The patient needs to be followed up with routine physical examinations after surgery every 6 months for 5 years and then annually as recurrences often present as pelvic, abdominal or pulmonary metastasis.
- If the patient had myomectomy for fertility preservation, then clinical examinations every 6 months after surgery with yearly MRI and chest X-ray should be done for next 5 years. Once the woman completes her family, hysterectomy is recommended to prevent recurrences.

Recurrence or Under Diagnosed LMS

The risk to recur is one of the hallmarks of uterine STUMP. The recurrence rates range from 8.7 to 11% irrespective of the type of surgery performed. Time to recurrence ranges from 2 to 194 months in the published data. This wide range is due to the unpredictable behavior of STUMP and the spectrum of possibilities of this neoplasm. In a review of literature by Rizzo et al[17] of STUMP patients with recurrence, 11 patients (25% of cases) had histology consistent with LMS. Considering this, it can be postulated that some tumors thought to be STUMP might actually have been underdiagnosed LMS and conversely some leiomyomas with unusual pathology may have been wrongly reported as STUMP. It is important to correctly distinguish between LMS and STUMP as the former is a very aggressive tumor with early recurrences and metastasis while STUMP is associated with delayed recurrences.

Zang et al reviewed 127 patients with leiomyomas ranging from benign to malignant and found that 21% of STUMP had recurred on follow-up. Ly et al had similar results with 12% of atypical leiomyomas recurring on follow-up. Guntupalli et al had a recurrence rate of 7.3% among 41 patients during a mean follow up of 45 months. Generally, STUMPs may recur as either STUMP or as LMS.

Although standard guidelines for treatment are not available, the common strategy for recurrence remains surgical treatment. Role of adjuvant therapy in the form of pelvic irradiation, Medroxyprogesterone, chemotherapy or gonadotropin-releasing hormone analogue is not clear as the clinical course of the tumor has been found to be similar in absence of such treatment.

Metastasis – Rare but Possible Entity

Metastasis of STUMP is rare, but a reported phenomenon. The lung has been the most common extra-uterine site for metastasis followed by the bone. Canciani et al. reported an isolated recurrence of STUMP 24 years after hysterectomy with metastasis to the lungs. Miller et al in a retrospective review identified 10 patients with benign metastasizing leiomyoma to the lungs. Shapiro et al. reported a case of STUMP tumor with metastasis to the humerus, while Kropp et al. also diagnosed a uterine STUMP tumor from a primary bone tumor.Rizzo et al in a review of all reported articles on STUMP with recurrence till May 2019, found that 15 out of 46 patients (33%) experienced

local relapse, with the pelvic area as the only involved site. The most common distant metastatic sites were found to be lung (15/46, 33%), bone (7/46), liver and peritoneum.[17]

Conclusion

Uterine STUMP has posed as an enigma for the last 3 decades since it was first mentioned by Kempson et al. Concerns regarding over or under diagnosis exist due to lack of specific diagnostic criteria,indolent clinical course and possible malignant potential. A multidisciplinary approach is mandatory, and future perspective studies should be undertaken to identify the molecular basis of STUMP using molecular biology techniques. The identification of key genes directly involved in the carcinogenesis of STUMP may suggest novel opportunities in the management of the disease and provide further information in understanding the process of carcinogenesis. To conclude it is suggested that a detailed pathological evaluation by experienced gynecological pathologists will go a long way in correctly diagnosing and managing such cases.

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High Grade Serous Carcinoma Ovary

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Introduction

Ovarian cancer is one of most lethal form of gynaecological malignancy. In the world as per GLOBOCAN 2018, the incidence rate of ovarian cancer is1.6%, with 29541new cases, accounting to 184799 deaths representing the 7th most common cancer in females.[1]

Recently, a 2-tier system in which tumors are subdivided into low-grade and high-grade has been proposed. This approach is simplistic, reproducible, and based on biologic evidence indicating that both tumors develop via different pathways. Low-grade serous carcinomas exhibit low-grade nuclei with infrequent mitotic figures. They evolve from adenofibromas or borderline tumors, have frequent mutations of the *KRAS*, *BRAF*, or *ERBB2* genes, and lack *TP53* mutations (Type I pathway). The progression to invasive carcinoma is a slow step-wise process. Low-grade tumors are indolent and have better outcome than high-grade tumors. In contrast, high-grade serous carcinomas have high-grade nuclei and numerous mitotic figures. Identification of a precursor lesion in the ovary has been elusive and therefore the origin of ovarian carcinoma has been described as *de novo*. More recently, studies have suggested that a proportion appear to originate from intraepithelial carcinoma in the fallopian tube. The development of these tumors is rapid (Type II pathway). The vast majority are characterized by *TP53* mutations and lack mutations of *KRAS*, *BRAF*, or *ERBB2*. Although both types of serous carcinomas evolve along different pathways, rare high-grade serous carcinomas seem to arise through the Type I pathway. Immunohistochemical stains for p53, p16, and Ki-67 for distinction of low- from high-grade tumors are of limited value but can be helpful in selected instances.[2]

	Low-grade serous carcinoma	**High-grade serous carcinoma**
Precursor lesion	Adenofibroma/ cystadenoma →APST → non-inv MPSC → inv MPSC	Tubal intraepithelial carcinoma*
Level of chromosomal instability	Low	High
Genes typically mutated	• KRAS • BRAF • ERBB2	*TP53*
Tempo of tumor development	Slow, step-wise	Rapid

Key: APST, atypical proliferative serous tumor; inv MPSC, invasive micropapillary serous carcinoma; non-inv MPSC, non-invasive micropapillary serous carcinoma; and *, Currently, precursor lesions in the ovaries or peritoneum have not been firmly established, and it appears that approximately half of high-grade serous carcinomas are associated with tubal intraepithelial carcinoma.

High grade serous carcinomas of ovary, fallopian tube and primary peritoneal serous carcinomas are now regarded as a single disease entity with a large proportion arising from fimbria of fallopian tube and some from Mullerian remnants in coelomic epithelium[3,4]. Few of the studies claim to show that the fimbriae are enriched in cells with stem cells like properties that may underlay all the ability to differentiate into structures resembling multiples tissues of Müllerian origin, including the endometrium and distal/proximal oviduct[5].

Dysregulation of p53 and disruption of normal G1/S transitions leads to poor DNA repair, leading to genomic instability and the characteristic of high copy number variability is essential for HGCS[6]. The proteins encoded by BRCA1 and BRCA2 are critical for maintenance of the double-stranded DNA repair pathway, homologous recombination repair. Loss of function of these genes requires p53 dysregulation for cellular viability which precedes serous tubal in situ carcinoma.

Germline mutations in the tumour-suppressor genes BRCA1 and BRCA2 also contribute to the increased risk of developing breast cancer in these same families. Compared to the normal population, BRCA1 mutation carriers have an estimated 44% risk of developing ovarian cancer by age 70, while this risk is up to 27% for BRCA2 mutant individuals. The cancers occurring in these women are usually

high-grade serous carcinomas, which manifest at an earlier age than in sporadic cases[7].

The most validated prognostic and predictive biomarker within high-grade serous cancers is germline mutation in either BRCA1 or BRCA2 and also somatic homozygous loss of BRCA1 or BRCA2

TCGA, Gene expression sets were found to segregate high-grade serous cancers into four descriptive groups: proliferative, mesenchymal, immune, and differentiated which are yet to be applied diagnostically and clinically(8).

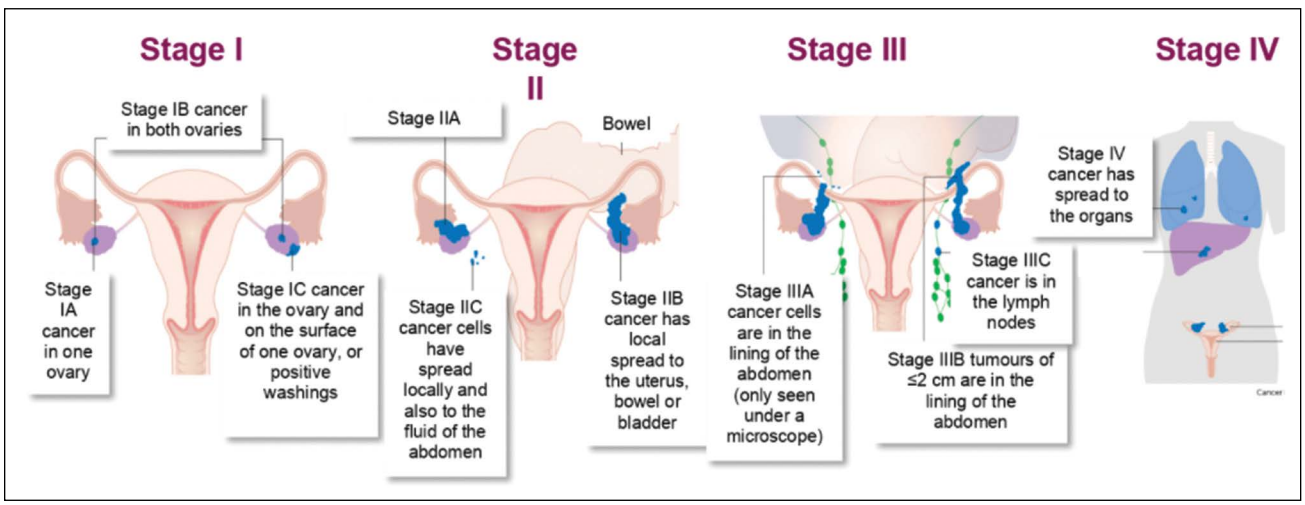
Management

Diagnosis

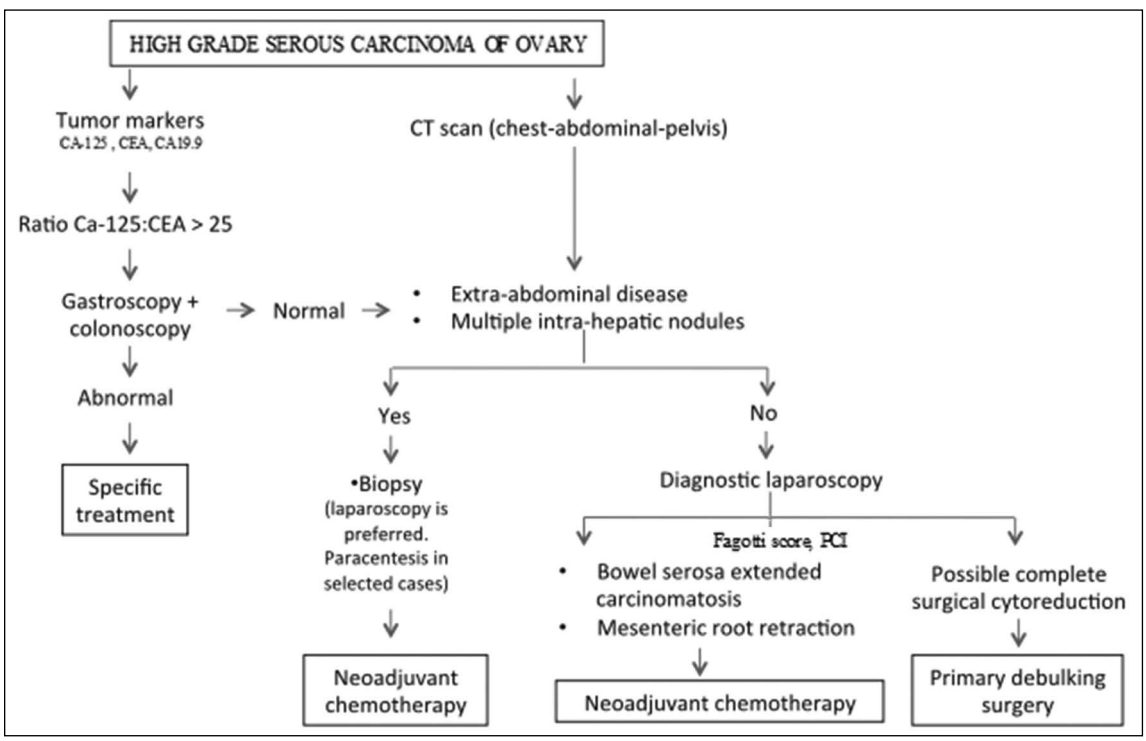
The symptoms are vague and typically are gastrointestinal and include abdominal pain, bloating, nausea, constipation, anorexia, diarrhoea and acid reflux for >12days /month. Any abnormal bleeding, unexplained loss of weight, excessive fatigue. At an advanced stage, respiratory symptoms might be present such as cough and dyspnoea.

If a diagnosis of EOC is suspected, the patient will be subjected to a pelvic and rectovaginal

Following confirmation of diagnosis, the extent of stage is determined (FIGO 2014)



Approach to management of High Grade Serous Ovarian Cancer



examination along with radiographic imaging such as transvaginal or abdominal ultrasonography, CT, MRI or PET. Blood levels of CA125, CA 19.9, CEA will be measured, which in combination with other tests, might be of diagnostic value. Image guided biopsy of tissue and cytology of ascitic fluid provides the diagnostic confirmation.

Decision to perform surgery is guided by tumor characteristics, patient criteria, surgeon criteria & institutional infrastructure.

Rationale for Surgical Staging and Cytoreductive Staging

A comprehensive staging detects occult metastasis in about 30% of patients. It helps to decide on the need of postoperative adjuvant treatment and helps to determine the prognosis of the patients.

Primary cytoreductive surgery leads to improvement of oncological outcome, reduction of tumor burden and improved drug diffusion during chemotherapy.

The goal of surgery in ovarian cancer is to achieve complete cytoreduction to no gross residual disease. To achieve optimal cytoreduction various procedures like peritonectomy, appendicectomy, cholecystectomy, splenectomy, partial liver resection, bowel resection, partial gastrectomy, partial cystectomy with ureteroneocystostomy and distal pancreatectomy can be done in addition to removal of primary tumor and omentectomy.

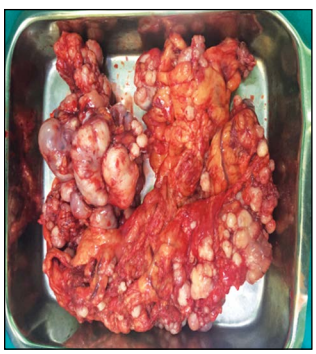


Figure 1: Omentum with tumor deposits

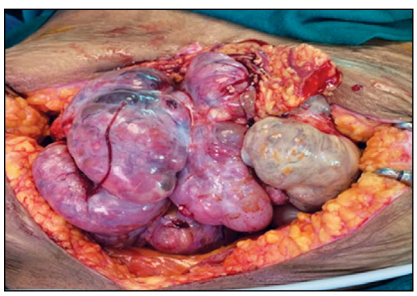


Figure 2: Bilateral adnexal mass

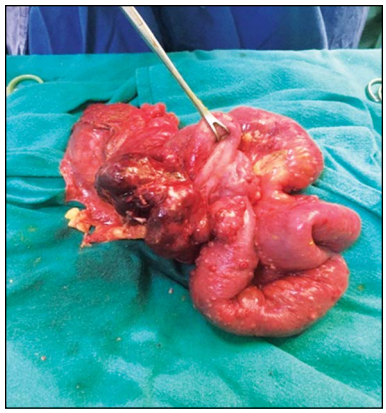


Figure 3: Resected small bowel segment involved by tumor

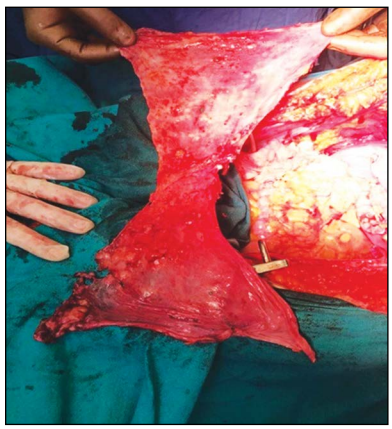
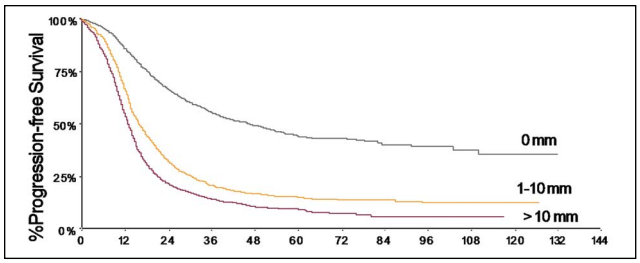


Figure 4: Resected bilateral subdiaphragmatic peritoneum

Role of lymph node dissection :Systematic pelvic (5%)and para-aortic lymph node(9%) dissection can upstage the disease in apparent early stage ovarian cancer, hence is advisable. Systematic pelvic and para-aortic lymhadenectomy in patients with High Grade Serous Ovarian Cancer with both intra-abdominal complete resection and clinically negative lymph nodes neither improved overall survival nor progression-free survival despite detecting (and removing) retroperitoneal lymph node metastases in 56% of the patients in LION trial, endorsing omitting of routine lymphadenectomy in such cases[9].

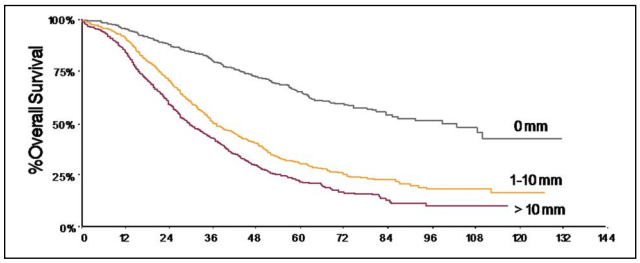
Evidence suggests that successful cytoreduction surgery is associated with improved progression free and overall survival confirming the fact that maximal cytoreduction leads to survival benefit. Optimal cytoreduction equalled an increase of mean weighted survival time of 11 months (50% increase). Each 10% increase in maximal cytoreduction equalled a 5.5% increase in median survival time[10].

PFS and OS were directly related to the size of the residual disease left behind after surgical effort[11].



	HR (95% CI)
1-10 mm vs. 0 mm	2.52 (2.26-2.81)
>10 mm vs. 1-10 mm	1.36 (1.24-1.50)

log-rank: p < 0.0001



	HR (95% CI)
1-10 mm vs. 0 mm	2.70 (2.37-3.07)
>10 mm vs. 1-10 mm	1.34 (1.21-1.49)

log-rank: p < 0.0001

Interval Debulking Surgery

Interval debulking surgery (IDS) in HGSC is considered to be an alternative treatment option to standard treatment in patients unable to undergo upfront debulking surgery or primary debulking surgery(PDS). NACT is defined as the chemotherapy performed prior to cytoreductive surgery. Confirmation of clinical diagnosis of ovarian cancer required by core biopsy or FNAC with IHC. In recent years, NACT-IDS has gained credibility as a valid therapeutic strategy especially for patients with advanced disease, poor general condition with massive pleural effusion, compromised nutritional status and unresectable bulky tumor.

Procedures mentioned in primary CRS should be done to achieve optimal debulking after completion of NACT. Various trials on role of NACT have been conducted on stage IIIc and IV carcinoma ovary comparing median PFS and OS in both the groups. EORTC and CHORUS showed both treatment strategies had similar overall survival and progression-free survival in women with International Federation of Gynecology and Obstetrics (FIGO) stage IIIC or IV tubo-ovarian cancer, and operative and postoperative morbidity was lower with neoadjuvant chemotherapy. All the studies including the ongoing Japanese GOG trial prove NACT - IDS to be non-inferior to upfront surgery.

Among patients with stage III epithelial ovarian cancer, the addition of HIPEC to interval cytoreductive surgery resulted in longer recurrence-free survival and overall survival than surgery alone and did not result in higher rates of side effects[12].

It is very important to emphasise the fact that with the proper selection of patients for primary CRS should be initial option in patients with stage IIIC and IV disease and good performance status, < 5 cm upper abdominal disease, retroperitoneal nodes as the only site of stage III disease. NACT may make the surgery more difficult and optimal debulking status achieved after NACT is different from that achieved after primary CRS (Pseudo-debulking).

Chemotherapy

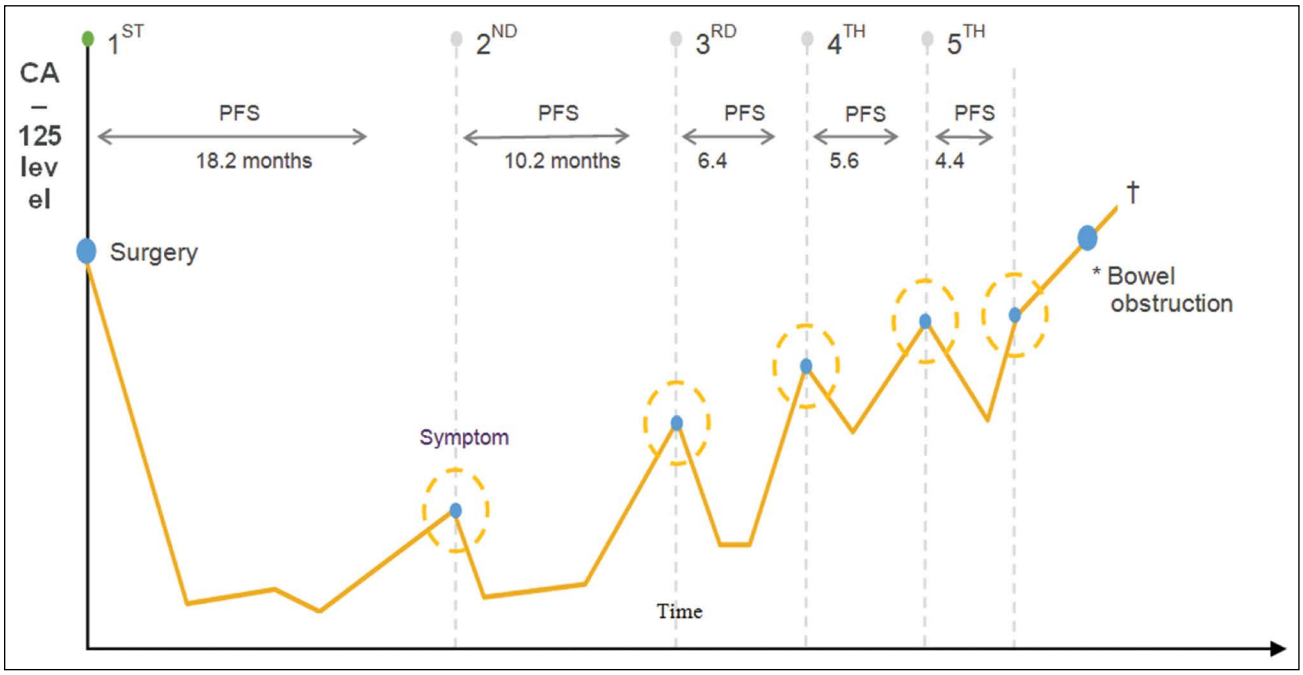
Following successful cytoreductive surgery, either primary or interval,patients with HGSOC are recommended to undergo adjuvant chemotherapy.

The combination of carboplatin area-under-the-curve (AUC) 5/6 and paclitaxel (175 mg/m2 intravenously, every 21 days) or dose dense method remains the standard approach in the first-line setting. Acceptable alternatives are the addition of bevacizumab to upfront carboplatin-paclitaxel regimen followed by maintenance therapy. Potential survival advantage for 6 cycles of chemotherapy for patients with serous histology[13].

Recurrence

It is estimated that 80% of these patients will eventually relapse at some stage. No single therapeutic agent is currently recommended as treatment of choice for recurrent cancer ovary. The goals of second-line treatment are to prolong survival, to postpone symptomatic disease progression, and to improve quality of life. Traditionally treatment for relapse ovarian cancer is guided by the sensitivity to platinum-based therapy. Patients sensitive or partially sensitive to platinum, defined respectively by a platinum-free-interval (PFI) > 12 or by a PFI of 6–12 months, are treated with combination chemotherapy, usually platinum-based. In patients relapsing with a disease that is platinum-resistant, a variety of

Patients Often Receive Multiple Treatment Lines with Ever Decreasing Periods of Remission Between Regimens of Cytotoxic IV Chemotherapy



alternative treatment modalities may be given, such as pegylated docetaxel, etoposide, liposomal doxorubicin, topotecan, gemcitabine, and with or without bevacizumab[13].

Secondary Cytoreductive Surgery

A number of studies have supported the role of secondary cytoreduction for resectable recurrent disease. The DESKTOP 3 trial included patients with positive AGO score, an Eastern Cooperative Oncology Group performance score of 0, ascites ≤ 500 mL, and complete resection at initial surgery. They found that OS was superior, at 61.9 months with complete resection versus 46.0 months among patients who did not undergosurgery[14].

The SOC 1 trial (NCT01611766) being conducted in China will assess progression-free and overall survival as primary endpoints. In addition, its secondary outcome is to validate the iMODEL risk model of patient selection criteria in platinum-sensitive recurrent ovarian cancer.

The National Comprehensive Cancer Network Guidelines Clinical Practice Guidelines in Ovarian Cancer recommends surgery as an option for patients who have relapsed more than 6 months after complete response to prior chemotherapy[13].

Novel Targeted therapy in Ovarian Cancer

Anti-angiogenic Agent

Bevacizumab in combination with chemotherapy has been extensively investigated in various settings of ovarian cancer treatment, including first-line treatment (GOG-0218, ICON7 studies), and treatment of recurrent ovarian cancer in platinum-sensitive patients (OCEANS study, and in platinum-resistant patients (AURELIA study). Overall, the addition of bevacizumab to chemotherapy has been shown to prolong PFS, with an acceptable tolerability profile and preserved quality of life. NCCN 2020 recommendation adding bevacizumab to upfront chemotherapy paclitaxel/carboplatin followed by maintenance therapy is category 2B.[13]

Poly (ADP-Ribose) Polymerase Inhibitors- (PARP)

HGSOC is characterized by widespread genomic instability and the majority of patients possess some deficiency in DNA repair pathways (germline or somatic), particularly those involving the repair of DNA double-strand breaks by homologous recombination. The proteins encoded by BRCA1 and BRCA2 are involved in this pathway along with many others. In patients with a deficiency in homologous

recombination, the cancer cells are over-reliant on the poly (ADP-Ribose) polymerase(PARP) mediated base excision repair (BER) of single-strand DNA repair, and its inhibition prevents cancer cells with deficient BRCA function from repairing chemotherapy-induced DNA damage, making them more vulnerable to cytotoxic agents, a concept known in oncology as synthetic lethality

Based on SOLO2 trial NCCN panel recommends Olaparib as maintenance therapy for those who received 2 or more lines of chemotherapy.[13]

Rucaparib-(ARIEL2 Trial) the NCCN panel recommends rucaparib as single agent therapy for women with recurrent ovarian cancer, irrespective of platinum sensitivity, who received 2 or more lines of chemotherapy and have BRCA mutations.[13]

Niraparib- (nova Trial) the NCCN panel recommends niraparib as maintenance therapy for platinum sensitive disease patients who received 2 or more lines of platinum-based chemotherapy.[13]

Conclusion

HGSOC is the most common ovarian cancer and possibly the most lethal with very high incidence of relapse. The majority of HGSOC cases are now understood to be derived from the secretory epithelial cells of the distal fallopian tube. With vague symptomology rarely it is detected in its early stages. The most effective treatment modality still remains upfront debulking surgery which provides the longest DFS and subsequent OS. The mainstream of patients will present with a disease that already has disseminated. The primary response to the frontline platinum-based chemotherapy is excellent. Differential degrees of DNA repair dysfunction have been identified in different molecularly characterized subsets of HGSOC that may lead to selected future targeted therapy.

Recently, PARP inhibitors and antiangiogenic agents are promising in the latest trials in recurrent settings.

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Contrast Enhanced Ultrasound in Gyanecological Practice

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Introduction

Gynecological practice has been transformed over the last 15-20 years with the help of evolving imaging modalities. A correct diagnosis is required by the clinician to determine the correct line of management. In patients undergoing surgery the pre operative evaluation is necessary to plan the extent of surgery. It also helps in explaining the patient about the condition and morbidities associated.

The most common imaging modality is Ultrasonography (USG), it defines the baseline features of the pathology. Transvaginal ultrasound (TVS) was introduced in 1985, which gives a better picture than the abdominal counterpart and is being used extensively for diagnosing uterine and adnexal pathologies since then. CT(computed tomography) and MRI(magnetic resonant imaging) are superior imaging modality but are more expensive and time taking and not available at low resource setting.

In the last few decades the imaging techniques have technological developments focussed on functional application, tumor biology and angiogenesis. Doppler is one such advancement in the field of ultrasonography. Doppler studies help in determining the blood flow along with the direction and the intensity of flow through various large and small vessels. Spectral analysis by Doppler helps us to predict the vascularity of the target area but it lacks the ability to detect blood flow at capillary level. Both 2-D and doppler have limited capacity in depicting perfusion at microvascular level(<2mm) and also in visualizing deep vessels(>10cm). The above two shortcomings by conventional methods of ultrasound limits their use in gynaecology, especially in determining cases of ovarian and endometrial cancers. To eliminate this limitation contrast enhanced ultrasonography (CEUS) is used.

Contrast enhanced ultrasound (CEUS) is a newer imaging modality using contrast comprising of gas microbubble. When compared to conventional 2-D USG and Doppler studies it shows superior imaging quality for diagnosis of utero-adnexal pathologies.

Modern contrast agents were introduced in 1996 mainly for echocardiography, vascular USG, Doppler, and whole abdomen ultrasonography in Europe and Asia. CEUS provided a detailed real time evaluation and quantification of microcirculation in the targeted area which was beyond the scope of Doppler Ultrasound.[1] Over the past decade, it has gained increasing credibility and popularity over conventional ultrasound as it is relatively easy to use in clinical practice and improves the detection and characterization of various diseases, reducing the need for additional imaging modalities like CT or MRI.[1]

It is difficult to differentiate focal adenomyosis from fibroid, endometrial hyperplasia from endometrial cancer, and benign and malignant adnexal masses on 2-D USG and Doppler and often requires evaluation by MRI. In these cases CEUS finds the utility, as size of microbubble of the contrast lies in range of 1-4 micrometer. This makes it smaller than red blood corpuscles (RBC) so that it can flow easily through the capillaries and gets easily eliminated via lungs[2]. The advantages of CEUS over conventional USG or Doppler are that it provides real time picture of blood flow and quantifies tissue perfusion too, with no exposure to radiation. Though the modality is still not validated, previous studies show promising results making it superior to 2-D USG and doppler with results comparable to CT.[2] CEUS is used worldwide for various diseases of liver, kidney, blunt trauma, however the role of CEUS in gynecological diseases is not clearly established by current guidelines and clinical practice. CEUS is an emerging modality and can be used as an alternative to CT and MRI which will be easier to use for target organ scanning, less time taking, cost effective and safer for the patient having hepatic or renal impairment where other contrasts are contraindicated. Apart from this, the

contrast microbubble used in CEUS which has no side effects on renal and thyroid function.

Contrast is also used for evaluation of tubal patency and uterine cavity as an alternative to Hysterosalpingography and this is known as Hystero salphingo contrast sonography (HyCoSy). CEUS has also been used to aid fibroid devasularisation in procedures like Uterine Artery Embolisation (UAE) and High Intensity Focused Ultrasound (HIFU). Other than these uses CEUS is found to be useful in cases of ovarian torsion where ovarian sparing was done. Flow of contrast can predict the restored vascularity post surgery. It can also detect Arterio-venous malformations (AVM) and retained products of conception.[3]

Contrast Enhanced Ultrasound (CEUS)

For sonography contrasts were first introduced in 1968 for use in echocardiography by Gramiak and Shah. From an unprotected, unstable room air bubbles contrast agent in sonography have evolved to a complex, stable, core-shell system. These modern contrast agents are widely in use since 1996.[1] Since then it has been widely used for vascular, hepatic and renal USG. However the use of contrast in gynaecological USG started very late but various studies have showed high sensitivity and specificity of CEUS as it can evaluate the microvasulature which is beyond the scope of conventional 2-D or Doppler USG.

Microbubbles used in CEUS have very high echogenicity and there is a great difference between the echogenicity of microbubble and the surrounding soft tissue. This difference in echogenicity provides a clear visualization of the structure and vasculature of the target organ.

Contrast may be a small air bubble or a more complex structure, commonly used as gas filled microbubble which is administered intravenously. General features of a contrast are as follows:

1. **Microbubble shell:** The shell material determines how easily the microbubble is taken up by immune system and it also affects the mechanical elasticity of the material. More hydrophilic material tends to be taken up more easily in circulation and reduces the time available for contrast imaging. It can be made up of albumin, galactose, lipids, and polymer.
2. **Microbubble gas core:** It determines the echogenicity of the microbubble. It can be made up of air, heavy gases like perflurocarbon or nitrogen.
3. **Size:** Diameter of the microbubble is between 1-4 micron.

   Various contrast agents available are:

   - **SONOVUE -** phospholipid shell and SF6 core
   - **OPTISON -** albumin shell and C3F8 gas core
   - **DEFINITY -** phospholipid shell with C3F8 core
   - **LEVOVIST -** galactose shell and nitrogen core
   - **ALBUNEX -** albumin with nitrogen core

Most commonly used contrast agent is **Sonovue** which is produced by Bracco, Germany. It contains Sulphur Hexafluride gas core in a phospholipid shell. The Sulphur Hexafluride gas is an inert molecule which doesn't interact with any other molecule in body and is excreted out of the body via lungs.[1] Contrast comes in the form of powder in a concentration of 8 microlitre/ml. This powder has to be dissolved in 5 ml of normal saline and shaken vigorously for few seconds. Shaking dissolves the lyophisilate and after reconstitution the contrast should be administered immediately and the efficacy of remaining content lasts for 6 hours.

CEUS evaluates capillaries less than 40 microns unlike Doppler. Owing to its physical property the contrast enhance the backscatter of waves by its high resonance. While performing USG in gynaecology a low mechanical index (MI) technique is used. When contrast agents are introduced into the system they undergo stable and asymmetrical oscillations and generate non linear harmonic frequencies when exposed to incoming ultrasound waves. These signature signals contribute to enhancement of signal from contrast agents and their distinction from surrounding tissues.[3]

Hence by using the contrast dynamic picture can be furnished. The contrast has the property to retain within the blood vessels that is why it is also known as blood pool contrast. The agent used in CT and MRI moves into the extracellular space until the concentration gradient is balanced between the intra and extra vascular space.[2]

Apart from this the dye used in CEUS is a microbubble which has no side effects on thyroid function and does not cause contrast enhanced

nephropathy. Hence it can be used safely in patients having hepatic or renal impairment where other contrasts are contraindicated. Contrast rapidly spreads into the circulation, after repeated passage the microbubble dissolves and is eliminated via lungs and the membrane is eliminated via liver, making it a renal safe contrast. [2]

When the contrast enters the circulation the entry of contrast agent is visualized under contrast specific mode to note the entry and enhancement of the media in the lesion. World Federation of Ultrasound in Medicine and biology (WFUMB) has issued guidelines for using contrast in liver disease. Also European Federation of Societies for ultrasound in Medicine and Biology (EFSUMB) has issued guidelines for non liver conditions but these guidelines does not include guidelines for using contrast in gynaecological disease.

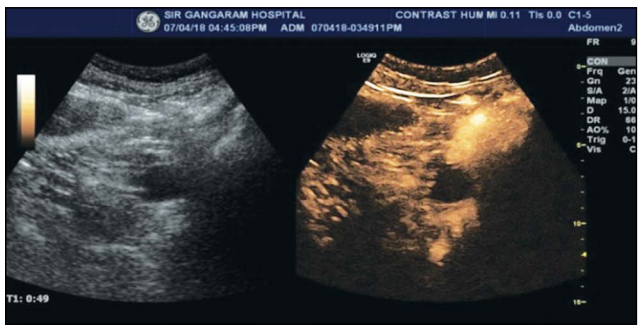
The reported studies of CEUS in literature are for:

1. **Adnexal Masses-**
   i. Benign
   ii. Malignant
   iii. Borderline
2. **Uterine Masses-**
   i. Fibroid
   ii. Adenomyosis
3. **Endometrial pathologies**-
   i. Hyperplasia (Benign)
   ii. Carcinoma endometrium
   iii. Endometrial polp
4. **Tubal patency- HyCoSy** (Hysterosalpingo Contrast Sonography**)**
5. **Diagnosing Arterio-venous malformations (AVM) and distinguishing between AVM and retained products**
6. **Diagnosis and prognosis of adnexal torsion**
7. **Guiding devascularisation procedure like HIFU, Uterine Artery embolisation**

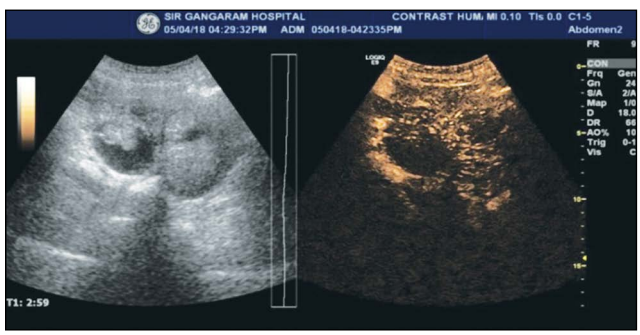
Characteristics of Adnexal Masses

Conventional ultrasound modalities were inadequate to pick up early malignant features. Earlier Sassone gave a scoring system to differentiate between malignant and benign cysts and various other authors kept on adding features to improve diagnosis of ovarian malignancy, few to name were ca-125, RMI, ROMA score. Then Timmerman gave the IOTA scoring system which was able to diagnose and differentiate between benign and malignant masses. However for inconclusive cases or unclassified cases there were no guidelines to establish diagnosis.

CEUS works on the principle of tumor angiogensis, a marker of tumor progression and metastasis and ability of CEUS to characterise microvasculature makes it an important tool in diagnosing ovarian masses. After administration of contrast agent malignant lesions show a faster uptake, a sustained enhancement due to retention of contrast and then a faster washout. Benign cysts show no enhancement of the cyst wall.

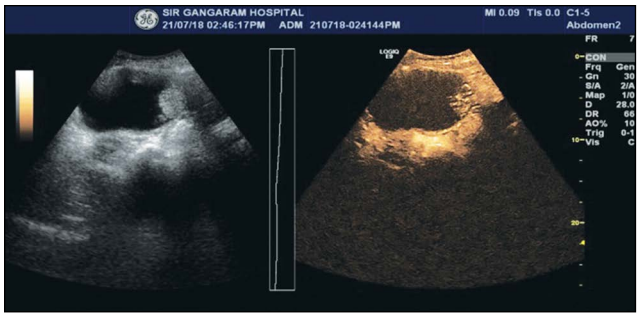


Pic 1: Benign cyst

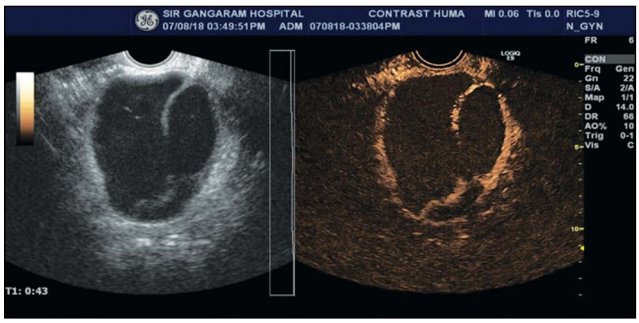


Pic 2: Malignant cyst

The hemorrhagic and endometrial cysts have septations and solid areas, which can mimic malignancy but on administration of contrast it lacks enhancement. Similarly borderline tumor enhancement was seen but it is slower and lesser than that seen in malignancy. In pic 3 there was minimal and diffuse enhancement of the intracystic solid mass and in pic 4 there was diffuse enhancement of septa but the flow of contrast was very less.



Pic 3: Borderline cyst with solid component

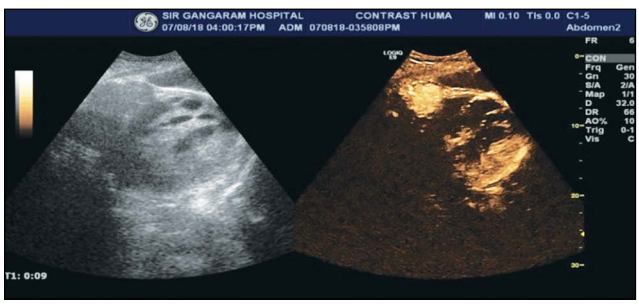


Pic 4: Borderline cyst with septa

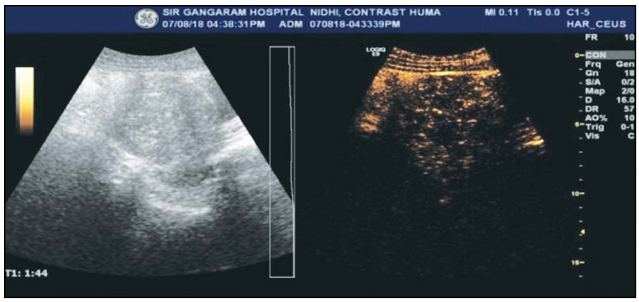
A meta anlaysis conducted by Liu et al[4] for ovarian masses showed sensitivity, specificity of 2-D was 92% and 85% and doppler had sensitivity and specificity of 93% and 86% CEUS had 97% and 92% respectively. Also in a systematic review and meta-analysis on CEUS for differential diagnosis of malignant and benign ovarian tumors by Ma et al[5] pooled sensitivity and specificity of CEUS were 93% and 95% respectively.

Characteristics of Uterine Masses

Uterine fibroid and adenomyoma when assessed by 2-D ultrasound can be differentiated as fibroid appears as hypoechoic, encapsulated with whorled appearance and adenomyoma has disordered echogenicity, ill defined margins with small cystic spaces within. However many a times it is difficult to differentiate between the two, and when in doubt CEUS plays the role. On administering contrast fibroids have a centripetal filling or the



Pic 5: Fibroid with centripetal flow, basket like appearance



Pic 6: Adenomyosis with centrifugal flow, moth eaten appearance

'basket like enhancement pattern' owing to its peripheral vascularisation. It can also differentiate degenerative changes in fibroid from sarcomatous change.

Whereas adenomyotic lesions have a diffuse or centrifugal enhancement of contrast with rapid uptake and clearing of the agent (Pic6), which was contributed to increased vascularity of the lesion. This is also described as typical moth eaten appearance of adenomyosis.

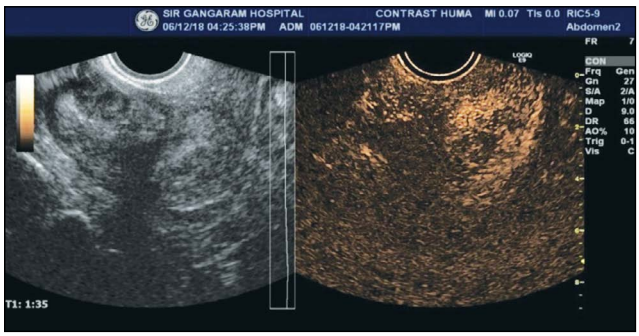
In a study by Lacelli et al[6] they concluded that CEUS was more effective in the diagnosis of adenomyosis than conventional and Doppler scan. Also basket like vascularisation has a 100% negative predictive value. Zhang et al[7] in their study on 96 patients with uterine mass had similar results. They reported diagnostic accuracy of CEUS as 96.7% and for 2-D it was 82.4%.

Characteristics of Endometrial Lesions

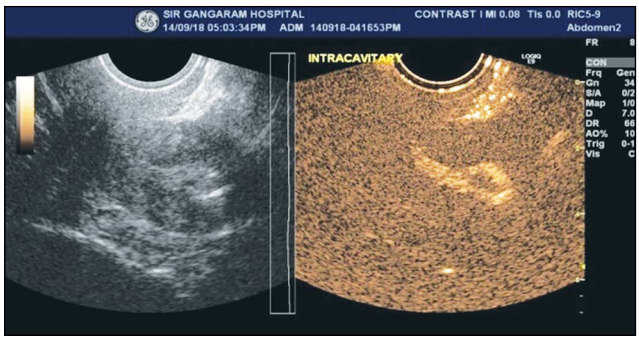
In women presenting with post menopausal bleeding and USG suggestive of thickened endometrium pre operative counselling and management strategy depends completely on the lesion being a benign hyperplasia, endometrial carcinoma or a benign polyp. It gives an idea to the clinician about the disease extent pre-operatively and before the preliminary histopathological report has been issued. So that the surgeon has a better picture in mind and plans the management of the case beforehand. By assessment of the vascularity CEUS plays a role in differentiating the lesion.

Benign hyperplasia shows features similar to normal endometrium with late enhancement and showing minimal or a lesser peak of enhancement as compared to myometrial layer and will be homogenous. Endometrial polyps show more rapid filling of contrast and a slower release of

contrast as compared to normal endometrium and vascular pedicle is better visualised with contrast administration.



Pic 7: Benign endometrial hyperplasia



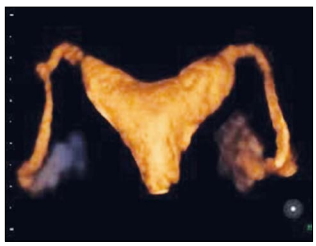
Pic 8: Endometrial cancer with early enhancement of the endometrium

In case of endometrial cancer 2D USG showed inhomogeneous endometrium which will not be clearly demarcated from myometrium, on CEUS inhomogeneous and hyper uptake of contrast with rapid washout is seen. It can detect the extent of myometrial invasion, it helps in determining the staging of endometrial cancer too.

Geng and Tang[8] in 2018 meta analysis on endometrial cancer and CEUS reported a sensitivity and specificity of 84% and 90%. In a study Liu et al[9] a group of 91 patients with increased endometrial thickness were investigated and evaluated by CEUS. Sensitivity and specificity of CEUS was 91.8% and 88.1%.

HYCOSY- Hysterosalpingo Contrast Sonography

Tubal patency assessment was done traditionally and most commonly by HSG, even though it has its own shortcomings like pain, discomfort, allergy to contrast, ovarian irradiation and false results due to tubal spasm. Then came SIS, using saline as a negative contrast agent, it had better delineation of adhesions and intracavitary lesions, however it is difficult to directly visualise saline and assess tubal lumen. In hycosy 1ml of contrast agent is mixed with 10 ml saline and instilled in uterine cavity, it delineates the cavity, tubal lumen and any obstruction can be well visualised, also the distance between the obstruction and cavity can be defined for planning further management. The contrast is non-toxic, non-irritating to the endometrium, tubal mucosa and peritoneal cavity and also associated with less pain.



Pic 9: HyCoSy

Contraindications of CEUS

1. Pregnancy- no clear cut consensus available for its use in pregnancy
2. Acute coronary syndrome, unstable angina- as circulation of contrast will be hampered
3. Respiratory disorders- it will interfere with removal of contrast microbubbles via lungs

We too conducted a study in our set up on 110 patients presenting with utero-adnexal pathologies and post menopausal bleeding with increased endometrial thickness on USG and compared the diagnostic accuracy of 2-D, Doppler and CEUS considering histopathology as the gold standard. The results were as follows:

1. Diagnostic accuracy of 2-D USG for uterine mass was 87.8%, Doppler was 85.13% and whereas for CEUS it was 93.2%.
2. For adnexal masses diagnostic accuracy of 2-D was 75%, Doppler as 81.25% and CEUS as 96.9%.
3. Diagnostic accuracy was found to be 75% with Doppler and 100% with CEUS for diagnosing increased endometrial thickness.

In all three conditions under study CEUS was found significantly better and superior to its conventional counterparts. CEUS is the next generation modality in the field of ultrasonography of gynaecological diseases and its popularity is increasing day by day. Its future lies in staging of gynaecological malignancies as it can map disease extent. However

it is not yet included in standard treatment guidelines and needs more studies for its use in gynaecological conditions.

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Role of Minimal Invasive Techniques in Vulval Cancer

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Introduction

Vulvar cancer accounts for about 4% of all gynaecological malignancies. The median age at diagnosis is 68 years. Recently, an increase in incidence in younger females has been noted which may be linked to increasing HPV infection. Ninety percent of vulvar cancers are of squamous cell carcinoma (SCC) histology[1]. According to the US SEER database, the 5-year survival rates range from 86% for localized disease (stages I/II), to 53% for regional or locally advanced disease (stages III/IVA), and only up to 19% for patients with stage IVB disease[2].

Basset in 1912 described the butterfly incision technique for the treatment of vulvar squamous cell carcinoma which involved radical vulvectomy with wide margins and inguino-femoral lymphadenectomy through a single incision. Better survival rates up to 74% were reported with this technique. However it was associated with increased perioperative blood loss, operative time and severe post-operative morbidity including wound break-down, lymphedema, physical and psychosexual morbidity[3]. Later Taussig described less aggressive approach with separate incisions for vulvectomy and inguino-femoral lymphadenectomy with comparable results but lesser perioperative and post-operative complications[4]. Nowadays, this 'triple incision' technique involving wide local excision or modified radical vulvectomy with 1cm tumour free margin along with bilateral inguino-femoral lymphadenectomy is the standard approach to treat vulvar cancer.

Inguino-femoral Lymph Nodes

Lymph node involvement is an independent survival predictor and most important prognostic factor. The risk of lymph node metastasis in patients with stage 1A disease is less than 1%[5]. The groin dissection or sentinel lymph node (SLN) evaluation can be omitted in these patients. Inguinofemoral lymphadenectomy is recommended for patients with stage IB/II disease as the risk of lymph node metastasis could be more than 8% in stage IB disease and even higher for stage II tumors[5]. For unilateral primary vulvar tumours of 2 to 4 cm diameter located 2 cm from midline, with clinically negative lymph nodes, unilateral inguinofemoral lymphadenectomy or SLN biopsy are appropriate options[6]. However, groin dissection is associated with high post-operative complications such as wound infection, wound breakdown, lymphocyst formation, skin flap necrosis and chronic lymphedema. Almost 20-40% of patients have wound complications and 30-70% experience chronic lymphedema. These complications are mostly related to conventional approaches and in order to minimize these complications, some surgeons have tried minimally invasive techniques for inguinal lymph node dissection such as sentinel lymph node biopsy and video-endoscopic inguino-femoral lymphadenectomy (VEIL).

Sentinel Lymph Node Biopsy

The principle behind sentinel lymph node biopsy is based on the hypothesis that if the first draining lymph node (sentinel lymph node) of a tumour is negative for tumour cells, then the other lymph nodes draining the area will also be negative. As only 25-35% of patients with early stage vulvar cancer will have metastasis to inguinal lymph nodes, this procedure can avoid extensive inguinal surgery and avoid long-term morbidity of thorough lymphadenectomy. Several prospective multicentre trials have evaluated this technique and shown its safety, feasibility and low groin recurrence rates. The technique involves use of intra-operative lymphatic channel mapping with technetium-99m-labeled nanocolloid lymphoscintigraphy and 1% isosulfan blue dye. The use of combination of radiocolloid and blue dye has better sensitivity than blue dye

alone. Technetium-99m-labelled sulfur colloid is more commonly used for SLN biopsy. It should be injected 2-4 hours before the surgery. About 4 mL of isosulfan blue dye is injected intradermally at four quadrants (2, 5, 7 and 10 o'clock position) around the tumour. The blue dye will be localized in the lymph nodes transiently for 30-60 minutes.

NCCN Recommendations for SLN Biopsy

- Patients should be carefully selected for SLN biopsy. Patients with clinical and radiologically negative nodes with unifocal vulvar tumour of less than 4cm size that are away from midline by at least 2 cm are suitable candidates for SLN biopsy.
- It should be performed by an experienced high-volume SLN surgeon using dual tracers (radiocolloid and blue dye) at a centre with adequate infrastructure.
- SLN procedure be performed prior to the vulvectomy, so as not to disrupt the lymphatic network between the primary vulvar tumour and the inguinofemoral lymph node basin.
- Gamma probe detection of the injected radiocolloid is recommended before groin incision to plan the location and size of the incision.
- If ipsilateral SLN is not detected, a side-specific complete inguinofemoral lymphadenectomy is recommended.
- If metastases of more than 2 mm in diameter is present in SLN, complete inguinofemoral lymphadenectomy should be performed.
- If ipsilateral SLN is positive, the contralateral groin should be evaluated surgically and/or treated with EBRT.
- Selective frozen section of sentinel node may guide the intraoperative decision regarding need for completion unilateral or bilateral inguinofemoral lymphadenectomy.
- SLNs should undergo ultrastaging for detection of low-volume metastasis.

GROINSS-VI, a multi-centric observational study, evaluated the safety and accuracy of SLN biopsy in 403 women with primary vulvar tumours less than 4 cm size[7]. If SLNs were reported negative on ultra-staging inguinofemoral lymphadenectomy was omitted. The 5- and 10-year recurrence rate in GROINSS-VI was reported as 24.6% and 36.4% for SLN-negative patients, and 33.2% and 46.4% for patients with a positive SLN (P = 0.03). The isolated groin recurrence rate was 2.5% and 8.0% for SLN-negative patients and SLN-positive patients at 5 years, respectively.

Video Endoscopic Inguino-femoral Lymphadenectomy (VEIL)

VEIL is the newest minimally invasive technique described to reduce the morbidity associated with open counterpart, to improve early recovery in post-operative period and yield a cosmetically better outcome. The technique of VEIL was first described by a uro-oncologist Bishoff et al, who demonstrated the technique in cadaveric models in 2003[8]. This technique is described in literature for management of cancers of penis, urethra, vulva and some melanomas of leg. Two types of endoscopic approaches are described in the literature based on the insertion's site of the trocars: (I) trocars inserted at the level of the lower limbs (limb subcutaneous approach: VEIL-L); (II) trocars inserted at the abdominal level (hypogastric subcutaneous approach: VEIL-H)[9]. The first case of bilateral VEIL in vulvar carcinoma was reported in 2012 by Huber et al[10]. Recently VEIL by single site and robotic variants has also been reported[11-12].

Technique of VEIL (Limb subcutaneous approach)[13]

- Performed under spinal, epidural or general anaesthesia. If bilateral VEIL is planned, then epidural or GA is preferred due to prolonged surgery duration
- Position the patient in low lithotomy position
- Apply intermittent pneumatic compression device to legs to prevent post-operative deep vein thrombosis
- Surface marking of the femoral triangle done for better orientation
- 1-1.5 cm incision performed 2 cm caudal to the apex of the femoral triangle for the camera port placement
- Scarpa's fascia is identified and subscarpa's plane is created either by sharp dissection or blunt finger dissection to create adequate space for insertion of secondary ports

- 5 and 10 mm ports are placed under the finger guidance, inside the dissected plane
- Right hand secondary port should be of 10 mm and left hand port of 5 mm for right handed surgeon for the ease of applying clips
- 10 mm camera port is inserted at the end and fixed to skin. Balloon port is preferred at camera port site to prevent carbon dioxide leakage
- All the ports are fixed to skin to prevent from slipping out
- Surgeon stands lateral to the patient's leg and monitor is placed on the contralateral side at the level of waist
- Pneumoperitoneum pressure is kept initially to 15–16 mmHg to assist in dissection
- Harmonic scalpel is useful in creating subscarpa's plane by piercing the fat mechanically to create the right plane
- Once subscarpa's plane is dissected upto the level of inguinal ligament, external oblique aponeurosis is seen.
- The boundaries of dissection are similar to that of the open approach. Dissect laterally and medially to the boundaries of femoral triangle.
- Carbon dioxide pressure should be reduced to 5–6 mmHg to prevent development of subcutaneous emphysema of the abdomen
- The superficial nodes are seen towards the floor. Small venous tributaries encountered may be divided using harmonic scalpel using coagulation mode.
- Dissection of deep fascia is started at the apex of femoral triangle
- The fat is carefully divided and the deep fascia is identified and cut. The saphenous vein is identified 2–3 cm medial to apex of femoral triangle and preserved, if indicated
- All the fibrofatty lymphoareolar tissue with deep fascia is divided along the lateral and medial border of the triangle.
- Deep fascia covering the femoral vessels is divided to see the lymphatics parallel to the artery and vein. Dividing these lymphatics could increase the post-operative lymphorrhea and lymphedema.
- Femoral nerve is seen lateral to the artery is identified and preserved.
- Saphenofemoral junction is exposed after opening the fascia lata, saphenous vein is dissected off the fibro fatty tissue to preserve the vein to reduce the risk of lymphedema. Deep pelvic lymph node dissection can also be performed if necessary
- Surgical specimens are removed in a laparoscopic bag through camera port
- Haemostasis is checked
- Suction drains are placed bilaterally through lateral port and continued till the output in 24 hours is reduced to less than 10–20 ml.
- Trocar incisions are closed in standard fashion

Modifications of VEIL

Robotic VEIL (R-VEIL)

Josephson et al, described the first case of robot assisted VEIL using Da Vinci system by 3 ports[12]. The technical steps are similar to laparoscopic route. The robot is located at 45 degree to the left of the patient and the assistant sits opposite to the robot on the right side of the patient. Three robotic ports (two 8-mm and one 10-mm) and one assistant ports are used. Lateral port is used either by robot for suction or retraction and by assistant for application of clips. Bipolar Maryland and monopolar scissors are the main instruments. The main advantages of robotic approach compared to laparoscopy are ease to the surgeon, 3 dimensional view with higher magnification and higher degree of freedom with instruments. However it is an expensive technology and adds to the cost of the surgery. At present, limited evidence is available in literature for this newer procedure.

Single-site VEIL (SSVEIL)

The technique was first described by Tobias-Machado et al in 2011 in a man with carcinoma penis[11]. A 1.5 cm incision 2 cm distal to the lower vertex of the femoral triangle was given and sharp and blunt dissection deep to the Scarpa fascia was performed. A 10-mm Hasson trocar was inserted in the first incision. The first, medial and lateral ports accommodated zero degree optics, the harmonic scalpel or the clip applier and the grasper, scissors, or a dissection device, respectively. The authors concluded that decrease in port size and number could decrease the post-operative morbidity in terms of reduced wound infection rate. reduced pain, reduced analgesia requirement, shorter

hospital stay, faster return to work and improved cosmesis. However, the technique is more surgically challenging, has longer operative time and needs special instruments. There is overcrowding of instruments leading to loss of triangulation and internal and external clashing of instruments.

Advantages of MIS

The literature evidence suggests that the postoperative complication rates are lower for VEIL (both approaches- VEIL-L and VEIL-H) compared to that of open approach. Various studies have demonstrated decreased post-operative morbidity, shorter hospital stay and faster return to routine activities without compromising the oncological outcome. Lu et al[14] reported laparoscopic groin node dissection (VEIL-H) in 15 patients with vulvar cancer. The authors reported a mean operative time of 91 minutes (range 80- 130 minutes), median estimated blood loss of approximately 6.3 mL (range 5-10 mL), and the mean number of harvested lymph nodes as 7.4. Only one woman with diabetes mellitus demonstrated vulvar wound infection. No skin necrosis was observed in inguinal region for all patients. Jain et al described the technique of 22 R-VEIL in 12 patients with squamous cell carcinoma of vulva[9] and concluded that R-VEIL allows the removal of inguinal lymph nodes within the same limits as the open procedure and has a potential to reduce the surgical morbidity associated with the open procedure. Only one groin recurrence was reported in this study.

Disadvantages

VEIL has certain disadvantages in terms of small working space, expensive equipment, lengthier operative time and steep learning curve. VEIL should only be performed by surgeons with expertise in laparoscopic techniques and familiarity with open inguinal lymphadenectomy.

Conclusion

VEIL has potential to replace open inguinal lymphadenectomy. The surgical incision is made away from inguinal folds and it decreases the postoperative complications in comparison with conventional open technique. Long-terms oncological outcomes are currently not available to come to any conclusion, although the initial results reported in the literature seem promising. Properly designed clinical trials should be initiated to compare VEIL and open technique.

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Breast Cancer and Pregnancy

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Introduction

Incidence and Definition

What should be considered breast cancer in pregnancy has been the subject of controversy over the past several decades. Pregnancy-associated or gestational breast cancer classically includes pregnant women found to have breast cancer either during pregnancy or up to one year. Some investigators chose to include patients up to six months after delivery[1] and others up to two years after delivery[2] while others have narrowed their definition to patients diagnosed during pregnancy or during lactation[3,4]. Some have further asserted that patients found to have breast cancer during pregnancy who actually experienced symptoms prior to pregnancy do not qualify as having PABC (Pregnancy Associated Breast Cancer)[5]

The inherent growth of breast cancer suggests that it would have been in situ for at least one year before being identified as a mass.

This trend could be explained by an increase in detection and awareness, but the delaying of childbearing to a later age is most often cited as the reason for the rising rate of PABC. It has thus been hypothesized that the incidence of PABC is rising because of the increased incidence of cancer with age.[6]

This suggests that although PABC occurs relatively uncommonly, it will be encountered more frequently by obstetricians if the trend to delayed childbearing continues.

Postpartum Breast cancer is the most common cancer in women across the globe. GLOBOCAN 2018 data suggests breast cancer to be the most common cancer amongst women in India accounting for 27.7% of new cases in females[7]. Mathur et al. in the national cancer registry data from India in 2020, projected a cumulative risk for breast cancer in women to be 1 in[8]. The proportional prevalence in younger age-groups in India is higher than the global average. The incidence of breast cancer is 25.8 per 100,000 women and is expected to rise to 35 per 100,000 women in 2026, according to the ministry of health and family welfare[9]. This data prompted us to discuss the subject to raise awareness amongst Obstetricians & Gynecologists who may be seeing more women with breast cancer in the future. In addition, antenatal breast examination must become the norm to identify masses early. Gestational breast cancer or pregnancy-related breast cancer is defined as breast cancer diagnosed during pregnancy or within a year after delivery. Using this classic definition, PABC represents a significant subset of total breast cancers. In the 25- to 29-year age group at least 20% of breast cancers are associated with pregnancy[10]. There are no randomized trials on the subject considering it is a rare event, scarcity of data in cancer registries and poor record keeping has led to a void of reliable information[10]. There are no screening recommendations also for this age group, except self-examination. Urgent need for establishing precise reporting systems in the available population and hospital based registries in Indian context has been emphasized in the past[11]. Expert recommendations are mainly based on data from retrospective case series. We aim to discuss the presentation, diagnosis and management of these patients followed by expert tips for obstetricians on high risk care for these women. We have tried to cover all salient points encompassing both – oncological and obstetric care in these women.

'Dual' Effect of Pregnancy

It is thought that pregnancy is protective and lowers the risk of breast cancer. But studies have found that pregnancy increases the risk of breast cancer initially following delivery and has a protective effect after a period of time and increased risk to be between 10 - 15 years following a first pregnancy.

The later the first pregnancy, the longer the duration of increased risk before the protective effect.

Risk of developing breast cancer lowers with multiple pregnancies, but the age at first birth remains the dominant influence on risk. BRCA1 and BRCA2 mutation carriers are not protected by early pregnancy from malignancy, but they do not have an increased risk of developing PABC compared with non-carrier women.

Presentation

No specific risk factors for pregnancy-related breast cancer are known. Genetic or environmental risk factors are known to be similar to those for age-adjusted breast cancer in the general population. Breast cancer in pregnancy most commonly presents as a painless lump[12]. Physiological breast changes associated with pregnancy, including engorgement, hypertrophy, and nipple discharge usually obscure diagnosis on examination. A high index of suspicion is therefore required. A palpable mass noted prior to pregnancy and that had increased in size at the onset of pregnancy, erythema and swelling, or inflammatory carcinoma- mimicking the presentation of mastitis or abscess. Other symptoms include discharge, nipple retraction, palpable supraclavicular lymph node or other palpable nodes, skin metastasis, Paget's disease, and distant metastases[13,14,15] In the postpartum period, another important presentation of breast cancer is the "milk rejection" sign, when a nursing infant refuses to breastfeed from a breast that harbors an occult carcinoma. This has been described as an important diagnostic sign because the carcinoma can be caught at an early stage. Unfortunately, the milk rejection sign is often disregarded by the physician and the carcinoma is diagnosed months later when a mass appears[16,17] bleeding from the nipple, unspecified nipple. This leads to a delay in the diagnosis, leading to detection of these cases in more advanced stages and subsequent poor prognosis. Mastitis during pregnancy, unlike during lactation, is an uncommon occurrence, and consequently inflammatory carcinoma must be ruled out before assuming that a pregnant woman has mastitis If mastitis persists in a lactating woman after a course of antibiotics, other causes such as abscess and carcinoma should be considered before introducing a new course of antibiotics[3]. A mass that persists for more than two weeks deserves further evaluation. It has been well-documented that pregnancy-related cancers present with poor pathological prognostic features and more metastases[18]. Thus the opportunity to do a clinical breast examination early in the antenatal period is warranted to timely identify cases.

Diagnosis

A clinically suspicious or persisting breast mass during pregnancy should be investigated by a core biopsy[19]. Another important point red flag should be an 'inflammed' breast and such cases should be thoroughly investigated. Ultrasonography of the breast and axilla is the primary investigation of choice with a high sensitivity and specificity[12]. Mammography provides less information because of pregnancy related changes and if ultrasound identifies an abnormality, MRI without contrast is used for confirmation. MRI with gadolinium contrast is contraindicated in pregnancy because of concerns of safety for use of gadolinium dye in pregnancy. There are certain contrast agents like gadobenate dimeglumine which are approved for use in pregnancy[12]. Core biopsy is the investigation of choice for histological diagnosis. Fine-needle aspiration should be avoided as physiological changes in pregnancy hinders histological diagnosis[13]. Metastatic work up would include chest X-ray with shielding, upper abdominal ultrasound and non-contrast skeletal MRI if bone metastasis is suspected.

Pathology

The differences in presentation of PABC and non-PABC on a cellular level can help to determine whether they are truly different entities, whether they are similar but modified by the hormonal milieu, or whether the cancers are identical but the pregnant state somehow modifies the patient's and the physician's propensity to be concerned about possible breast cancer. Age is one of the main determinants of the histological type of PABC. Infiltrative ductal carcinoma is the most common histology seen in pregnancy related to breast cancer. Poor pathological features like higher grade, larger tumor size, advanced stage and nodal positivity are much more common in these patients. This is probably attributed to delayed diagnosis of breast cancer in pregnant patients. Usually these tumours

are found to be ER/PR/HER2/neu-negative[13]. Histology of breast cancer is the same in pregnant and non-pregnant women.

Estrogen Receptor Status

The estrogen and progesterone receptor status of tumors has also been evaluated. Often, studies have reported PABC as having negative ER/PR status[21,22] This difference could be due to a technical difficulty in determining ER/PR status during pregnancy. Because of the largely retrospective nature of these studies, older techniques like the ligand binding assays were used to determine ER/PR status. These assays measure unbound ER/PR receptors to identify positive tumors and may therefore be falsely negative secondary to the high estrogen and progesterone.

levels found in pregnancy that saturate the ER/PR receptors. This theory is strengthened by a recent study using ligand binding assays, which found a significantly decreased ER-positive status in pregnant women with breast cancer compared to postpartum women with breast cancer, whose serum levels of estrogen and progesterone have returned to baseline[40]. Another important point that could partially explain a trend for decreased ER-positive and PR-positive tumors is the over-representation of BRCA mutations in PABC, which most often lead to ER-negative and/or PR negative tumors.[23]

Delayed Diagnosis

The delay in diagnosis could be due to false reassurance and by reluctance by clinician to undertake invasive diagnostic procedures. The risk of delaying treatment for one-month delay in diagnosis with an early stage breast cancer (65-day doubling time) increases the risk of axillary lymph node involvement by 1.8%[24].Delay in diagnosis by asking patients when they first experienced the symptoms that led to the diagnosis, has now been dropped, and newer studies evaluate whether or not there has been a delay between diagnosis and treatment[25]. Evaluating delay in treatment has the benefit of being more objectively measured, since it does not rely on patient recall.

Stage of Disease

In the majority of studies, the PABC groups had more advanced clinical and histological tumor sizes, TNM classification. These women with PABC have more advanced disease at presentation. Zemlickis et al.[20] noted that pregnant women with breast cancer had a risk of metastasis that was over two-fold higher than their age-matched control group.

Treatment

Principles of management are guided by tumor factors and gestational stage. Patient's and her partner's wishes also play an important role when continuation or termination of pregnancy is to be decided. Multi-disciplinary team will include high risk obstetrics specialist, surgical oncologist, neonatologist and oncofertility expert. Treatment protocol is similar to treatment in non-pregnant patients.

Each treatment plan has to very individualized to maximize the efficacy of treatment and minimize toxicity to mother and the developing fetus.

Treatment Plan

a. Termination of pregnancy

Termination of pregnancy does not affect the outcome of breast cancer. There has been no effect seen on survival or oncological outcomes if the pregnancy is continued and treatment protocols are adhered to[25]. The decision to terminate pregnancy is guided by patient's wishes considering the number of children she has and her future fertility desires. If poor prognostic factors are present, patient can be counselled regarding the same but the ultimate decision is that of the patient.

b. Surgery

For women in their second trimester, whose pregnancy has not reached viability, fetal heart tone monitoring would also be done, if pregnancy is after viability, however fetal monitoring may also be done.

Mastectomy and axillary clearance can be done in all three trimesters of pregnancy. Breast conservative surgery (BCS) can be done only in second and third trimester. There may be a situation where a woman is diagnosed late in her third trimester and is able to delay all cancer treatment because she is close enough to delivery. However, in such patients with aggressive subtypes, delaying treatment even

a month or 2 may allow disease to rapidly progress. Adjuvant radiation therapy is required for all BCS surgeries. This can be deferred by use of chemotherapy which is contraindicated in first trimester of pregnancy. Breast reconstruction if foreseen to be a long-duration procedure can be done as a second stage procedure to avoid prolonged exposure to anesthesia.

Sentinel Lymph Node Biopsy

For sentinel node dissection technetium based detection is the only method to be used as dye method using iso-sulfan blue is contraindicated in pregnancy. The estimated absorbed doses of technetium have been found to be below the fetal threshold absorbed dose, even under the most adverse conditions. Usually, short protocol technetium strategies have been safely conducted and reported[26]. From obstetric point of view, fetal heart monitoring and uterine tocometry are advisable during surgery.

Given the relatively small number of patients diagnosed with cancer during pregnancy, it is not likely that large or randomized studies will ever definitively describe the safety of SNB in pregnancy. Thus, the strongest data available come from cohort studies such as the one from Dana-Farber/Brigham and Women's Cancer Center, Boston, MA[36] here, which, although reassuring, is limited by small numbers and lack of follow up of children's outcomes. Based on the presented data, as well as a lack of strong evidence to support theoretical concerns, SNB appears to be both a safe and accurate procedure in this population.

Nicklas and Baker[27,35] suggest that the SLN procedure with TSC scan be safely performed in pregnancy, with negligible risk to the fetus, because the entire radioisotope stays trapped at the site of injection or within the lymphatics until decay occurs, and the exposure to the fetus is essentially zero.

c. Radiotherapy

Partial or whole breast radiotherapy is contraindicated and is best deferred until after delivery, unless it is used for life-saving issues or to preserve organ function, for eg spinal cord compression.

Adjuvant radiotherapy is not considered an urgent procedure and should be postponed until after delivery. Delaying treatment after 12 weeks, however, can increase the likelihood of axillary metastases by 0.028% to 0.057% per day and a delay over 6 months can increase the risk of local recurrence.

d. Chemotherapy

For pregnancy-related breast cancer, the indications to administer chemotherapy should follow the same guidelines as in non-pregnant patients. Physiological changes in pregnancy include increased plasma volume, decreased albumin concentration and presence of the amniotic fluid as a third space. All these lead to variations in pharmacokinetics of chemotherapeutic drugs. Most of the chemotherapeutic agents cross the placenta. Chemotherapy can be used in adjuvant or neoadjuvant settings. Indications for use of chemotherapy depends on the stage of disease and to defer radiotherapy if needed. Various standard regimens used are fluorouracil and epirubicin or doxorubicin plus cyclophosphamide, or epirubicin or doxorubicin plus cyclophosphamide and paclitaxel or docetaxel although safety of epirubicin has been debatable[12]. For fetal safety, chemotherapy is contraindicated in first trimester of pregnancy. As per expert recommendations, chemotherapy can be safely started from 14 weeks of gestation. It is safe to administer chemotherapy in the second and third trimester. Minimum interval of 3 weeks is required between last dose of chemotherapy and delivery to avoid maternal and fetal chemotherapy induced-cytopenia[21]. Hormonal agents are contraindicated for use in pregnancy. Use of tamoxifen is associated with birth defects including craniofacial malformations, ambiguous genitalia, and fetal death[12]. Oral aromatase inhibitors are also contraindicated. Similarly use of biological agents like transtuzumab is not safe in pregnancy.

Hormone Therapy

Tamoxifen is not used until after delivery. It is associated with oculo-auriculo-vertebral dysplasia (Goldenhar's syndrome) and ambiguous genitalia. Because of unknown transmission of the drug in milk, it is also contra-indicated in breastfeeding. Long-term effects of the drug on female offspring are unknown.

Prognosis

Pregnant women are less likely to be diagnosed with stage 1 but two and a half times more likely to be diagnosed with advanced disease than non-pregnant women. This often leads to a poorer prognosis in these patients. Not much data is available in this regard.

Expert Tips on Managing Pregnancy with Breast Cancer

Systematically screening all pregnant patients with a breast examination - during the first prenatal visit or early in the pregnancy. On the prenatal sheets there should be a dedicated section for breast examinations.

Pregnancy monitoring: Pregnancy-related breast cancer women should be registered with high risk obstetrics clinics. Pregnancy should be monitored as in any high-risk case but with special consideration for serial fetal scans for growth and ruling out any structural malformations. Aim of delivery should be kept >37 weeks of gestation as consequences of prematurity are well known. Last dose of chemotherapy should not be given after 34 weeks of gestation.

Delivery and post-partum: The timing of the delivery is the balance between fetal lung maturity and appropriate time for oncological therapy. It is recommended that the timing of delivery be approximately three weeks after the last dose of chemotherapy[28]. Placenta should be sent for histopathological examination to rule out metastases, which is rare but reported[29]. Chemotherapy and radiotherapy may be started as soon after delivery. Timing of chemotherapy after caesarean section can be decided by the medical oncologist, with interval being at least a week.

Breast-feeding: Breast-feeding is contraindicated if patient is on chemotherapy. Drugs for inhibition of lactation should be prescribed for such cases. In cases where chemotherapy is not required, breast-feeding can be safely initiated from unaffected breast.

Pregnancy outcomes: Amant et al. in a study of 129 children born to mothers diagnosed with cancer during pregnancy, over 50% of whom had breast cancer - cardiac, cognitive, and general development after a median of 22 months was found equivalent with controls matched for gestational age. Median gestational age of the children born to women with cancer was 36 weeks. There was a non-significant trend towards higher proportion of small for gestational age birth infants born to women with cancer (22 % Vs 15 %), particularly if they were exposed to chemotherapy or radiation[30]. In another cohort study of 1170 pregnant women with all types of cancer, 39 % of whom had breast cancer - 88 % of pregnancies resulted in live births and almost 50% of these deliveries were preterm[31].

Genetic counselling: Genetic counselling should be provided to all pregnancy-associated breast cancer patients. Approximately 10% - 20% of breast cancer cases show familial clustering. There is a high likelihood of pregnancy associated breast cancers to be hereditary as these are younger patients and triple negative. BRCA1 or BRCA2 genes have been primarily attributed to be the inherent mutations in hereditary breast cancers and genetic testing for same is recommended[32]. The National Comprehensive Cancer Network (NCCN) guidelines recommend that women aged ≤60 years with triple negative breast cancer should be referred for genetic counselling[33].

Future Pregnancy

There is evidence that pregnancy after breast cancer does not lead to increased risk of recurrence and may even improve survival, although these findings could be due to the 'healthy mother effect'. Large matched multicentre retrospective studies including more than 1000 patients confirmed that pregnancy after oestrogen receptor (ER)–positive breast cancer was not detrimental, at least during the first 5 years following pregnancy.[37] The latest ESMO guidelines also "do not discourage pregnancy following breast cancer diagnosis irrespective of the ER status".

Nonetheless, the chance of subsequent pregnancy is nearly 70% lower when compared with the general population, probably secondary to frequent treatment with gonadotoxic chemotherapy, prolonged treatment periods with tamoxifen in patients with hormone sensitive disease, and also a general misconception that pregnancy could stimulate cancer recurrence given that it is a hormonally driven disease. The chance of recovery of menses is higher for patients under 40 years of age and the use of taxane based chemotherapy.

"Consult Before Conceive"

A multidisciplinary approach is recommended before planning a pregnancy. Patients with metastatic disease are advised against pregnancy due to their_limited life expectancy and possible compromised treatment of disease. Interruption of full-course tamoxifen may have detrimental effects on breast cancer outcome. If, however, a woman is willing to accept the risk, interruption after 2 to 3 years of tamoxifen may be considered to allow pregnancy. Tamoxifen should be stopped for 3 months before trying to conceive. Latest ESMO guidelines "strongly encourage the resumption of tamoxifen following delivery".[37]

Embryo or Oocyte Cryopreservation

Main method to preserve female fertility. Ovarian stimulation is carried out before commencing chemotherapy, but may result in relative delay in oncological treatment and increase serum oestradiol levels. This may be of concern in hormone_driven tumours like breast cancer. Laparoscopic ovarian tissue sampling and freezing before treatment are considered experimental. When needed, re-implantation of ovarian tissue in the pelvis after thawing may be a unique option for young girls with cancer. Over 60 pregnancies have been reported.

Summary

- Treatment of breast cancer during pregnancy is possible
- Termination of pregnancy has no impact on survival or any oncological prognostication
- Clinical breast examination should be made mandatory on prenatal or first natal visit
- Ultrasonography of the breast and axilla is the primary investigation of choice
- Principles of oncological treatment are similar to those in general population, with a special care about foetus
- Surgery can be done in all stages of pregnancy, mastectomy and BCS, both are feasible options for treatment
- Chemotherapy is contraindicated in first trimester of pregnancy, best avoided till 14 weeks of gestation
- Minimum interval of 3 weeks should be present between last dose of chemotherapy and delivery
- Radiotherapy is contraindicated
- Pregnancy management should be done in High risk Obstetrics Clinic
- Breast-feeding is to be avoided with chemotherapy
- Tamoxifen, aromatase inhibitors & Transtuzumab are contraindicated
- Consult before conceiving
- Most of recommendations are good clinical practices based on case-series and reports

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Quality of Life after Genital Malignancies

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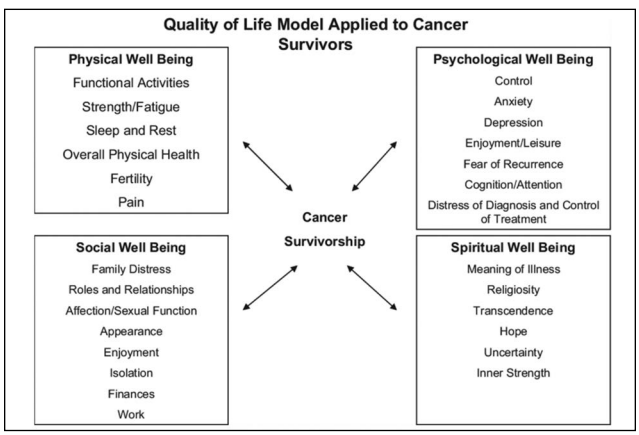
The result of any intervention is determined by its impact on the quantity and quality of life, which is measured against the maternal and psychological costs. Previously survival time or the quantity of life was supposed to be the best indicator of treatment. Time added by therapy is of sufficient value to justify its cost and to examine the value of therapies that do not add time to life, but appear to life is difficult to define. It can mean different things to same person at different points of time.

Quality of life is generally recognized as a subjective multidimensional concept that places emphasis on the subjective experience of various aspects of life. The term health related quality of life is often used to describe quality of life. Survivorship is a process that starts at the moment of diagnosis and continues until end of life. It is the experience of living with through or beyond cancer.

Phases of survivorship are:

- Acute stage
  - o Diagnosis
  - o Treatment
- Extended stage
  - o Remission
  - o Maintenance
- Permanent stage
  - o Long-term survival
  - o Cure
- Final stage
  - o End of life



Gynecologic oncologist is in a unique position to function collectively as a primary care provider, surgeon, radiation oncologist and chemotherapist allowing comprehensive transfer of treatment with emphasis on quality of life (QOL) of patient.

Quality of life information should play an important role in clinical discussion making. Two approaches are used to asses QOL:

- Outcome of treatment
- Preferences / utility assessment

Quality of life issues relating to gynaecological malignancies

a. General issues

b. Disease specific issues

General Issues

Various psychosocial and physical concerns that are common to patients with different gynaecological malignancies have been studied. Robert & colleagues found fear, difficulty in communicating feelings and social isolation to be common in 108 patients with different gynaecologic cancer. 63% patients reported some form of fear, including fear of pain, dying, losing control or becoming dependent on other.

Steginga and dunn reported 49% incidence of depression, anxiety and fear of dying in 82 patients studied. 50% of there 82 patients had symptoms of fatigue, pain, bladder dysfunction and vaginal dysfunction.

According to Lamb et al 50% of patients treated for Gynae cancer may suffer from some type of sexual dysfunction. A study by Guidozzi et al found that upto 80% of ovarian cancer patients experienced a decline in frequency of sexual activity after their diagnosis.

Disease Specific Issues

Approximately one-third of patients reported significant distress from treatment related infertility. Lee et al reported malignant ureteve

obstruction in 55% patients with advanced stage cervical cancer, urinary diversion can relieve urinary obstruction urinary diversion was felt to result in acceptable quality of life, 64.7% patients with local regional spread of cancer and a median survival of 5.6 months. Anderson & Hacker found that pelvic exenteration patients experienced long-term distress and chronic sexual dysfunction including decreased sexual desire and frequency of sexual activity.

Guidozzi surveyed 28 patients with advanced ovarian cancer and found that most of the patients reported deterioration in life areas during their first year of care that was not related to their response to therapy 96% of patient said the effects of chemotherapy were more debilitating than surgery. In 2nd year of follow up there was improved quality of life in-patient with no evidence of persistent cancer.

Patient Preference in Treatment

Patients feel the toxic side effects of chemotherapy more distressing than surgery

Various Indices used for measuring quality of life

a. Psychometric measure:
    1. Quality of life Index.(QOLI)
    2. Functional Living Index-Cancer(FLIC)
    3. Functional assessment of cancer therapy (FACT)
    4. Cancer rehabilation Evaluation system short form(GARES-SF)
    5. European organisation for Research and treatment of cancer quality of life questimaire (EORTC- QL2 C30)
    6. Medical outcome study (MOS)
b. Utility Measures
    1. Quality of well being scale.
    2. Quality adjusted time without symptoms and toxicity.

Comprehensive care of a woman with gynecologic cancer involves:

- Anti-cancer treatment
- Good symptom relief
- Personal & family support

Palliative care is widely advocated for people with eventually fatal illness. It facilitates comfort with dignity in personal rehabilitation and development. Till date no study has compared palliative chemotherapy versus the best supportive care regimen in the group of patients. Payne in 1992 reported on QOL that chemotherapy received at home was better than in hospital and concluded that location of CT had a significant effect on patient's QOL.

Doyle & associates found a significant discrepancy in terms of information provided and patients' expectations regarding the outcome of palliative CT. The reason of discrepancy given is that patients may not wish to acknowledge the possibility of dying from the disease as they may have high expectations.

Patient education, advice almost regular exercise, modification of activity and rest patterns, adequate nutrition and hydration are the important aspects for the management of cancer related fatigue.

About pain the recommended clinical approach is to ask, assess, believe, choose pain control options, deliver intervention in a timely logical, coordinated fashion and empower patients and their families.

Nausea & vomiting also have a high prevalence in advanced cancer patients. Agents used to control nausea and vomiting have different mechanisms of action and may be used in combination for better controls. Meloclopramide, $5HT_3$ antagonists, steroids and cannabinoids are used for controlling nausea & vomiting.

Constipation is highly prevalent in patients with advanced cancer. 90% of patients receiving opioids have difficulty passing stool. So the cardinar rule should be to write opioid with laxation also at the same time. Hypercalcaemic and Hypokalemia further lead to constipation.

Diarrhoea is a common complication of pelvic radiation. It can be managed with anticholinergic drugs.

The most important tool in caring for patients and their families is effective communication. Breaking the bad news is a difficult and emotionally laden lost for the physician.

The physician is uniquely poised to encourge and reinforce the patients hope without giving false or insincere reassurance, one study reported that only 5% patients stopped fighting after receiving a

poor prognosis with no medically recommended treatment options left.

The role of palliative surgery in the treatment of gynecologic cancer is that once the disease progresses, the goal changes from cure to prolongation of life with an emphasis on QOL during the remaining time.

The cancer diagnosis affects the patient's in following issues:

- Profound sense of loss
- Physical changes in a woman's body may be a barrier to physical intimacy between patient and her partner
- In a pre-menopausal woman at the time of diagnosis and loss of reproductive function can be devastating as compared to cancer diagnosis in older woman
- Breaking news to children
- Professional role of woman may be diminished

End of life issues affect the care of a woman with gynecologic cancer.

Cancer pain can be managed effectively by:

- Asking assess pain systematically
- Believing in the patient and family
- Choosing pain control options
- Delivering intervention
- Empowering patients and their families

Psychosocial and spiritual interventions can be tailored to enhance not only QOL for cancer survivors, but may have additional benefit of improving neuroendocrine and immune functioning leading to positive effects.

End of life decision making is based on three values central to human relationships:

- Patient benefit
- Patient self determination
- Ethical integrity

Hospice focuses on home care and is limited to patients with life expectancy of six months or less with willingness to sign a form acknowledging the desire to enter the programme.

Pallliative care programmes offer faster identification with hospice, home care or important programs.

Hospice in USA is a government regulated organisation or program for dying persons and their families that typically focuses on home cure with life expectancy of 6 months or less, focus on comfort measure, general preferences for care at home, a willingness to sign a form acknowledging the desire to enter this program and to focus on health insurance that cover hospice.

The challenge that palliative care faces today is to avoid orthodoxy while moving toward greater unanimity, about the nature of the field with improved standards for palliative care professionals and programs.

In conclusion advances in the measurement of quality of life among cancer patients makes it possible to better understanding the impact of diagnosis and treatment on women with gynaecological cancer.

Journal Scan

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The Vaginal Microbiota, Human Papilloma Virus and Cervical Dysplasia: A systematic review and network analysis

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Abstract

Introduction: The vaginal microbiota in women is mainly of Lactobacillus species, which create a low pH environment which is protective against exogenous bacteria and viruses by producing lactic acid, bacteriocins and biosurfactants. The disturbances in vaginal microbiota can cause bacterial vaginosis [BV] characterized by overgrowth of non- Lactobacillus microbes, typically anaerobic bacteria. BV is associated with pelvic inflammatory diseases and adverse pregnancy outcomes.

New culture independent molecular techniques have categorized vaginal microbiota into major community state type [CST] defined by the relative abundance and diversity of the identified species. These CST are broadly divided as Lactobacillus dominated CST [Lactobacillus crispatus, gasseri, iners, jensenii] and non Lactobacillus CST with low numbers of Lactobacillus species and an increased diversity of anaerobic bacteria or a mixture of aerobic and anaerobic bacteria.

Human papilloma virus [HPV] is one of the most common sexually transmitted infection; however most of the infection resolve after a few months. Persistent infection with HPV can lead to cervical dysplasia or cancer. Several smaller studies have suggested that there is an association between changes in the composition of microbiota and and infection with HPV. Women with a certain specific microbiota may be more prone to HPV or show a rapid dysplasia progression and therefore require closer follow up and more advanced treatment.

Objective: To assess how specific cervico-vaginal microbiota compositions are associated with HPV infection, cervical dysplasia and cancer, a systematic review and meta-analysis was conducted [registered in PROSPERO: CRD 42018112862]

Search Strategy: PubMed, Web of science, Embase and Cochrane database.

Selection Criteria: All original studies describing atleast two community state types of bacteria [CST], based on molecular techniques enabling identification of bacteria, and reporting the association with HPV infection, cervical dysplasia or cancer were included.

Data Collection and Analysis: For the meta-analysis, a network map was constructed to provide an overview of the network relationships and to assess how many studies provide direct evidence for the different vaginal microbiota composition and HPV, cervical dysplasia and cancer. Thereafter the consistency of the model was assessed and the forest plots were constructed to pool and summarize the available evidence, presenting odds ratio and 95% confidence intervals.

Main Results: Vaginal microbiota dominated by non Lactobacillus species or Lactobacillus iners were associated with three to five times higher odds of any prevalent HPV and two to three times higher for high risk HPV and dysplasia/ cancer compared with Lactobacilli crispatus.

Conclusions: These findings suggest an association between certain bacterial community types of the vaginal microbiota and the HPV infection and HPV related diseases. This may be helpful in guiding treatment options or serve as biomarkers for HPV related disease.

Strengths and Limitation

- First meta-analysis to examine if different CSTs defined by molecular techniques are associated with HPV related infection. Cervical dysplasia and cancer.
- More objective and quantifies the risk of different vaginal microbiota combinations.
- The statistical heterogenicity was low in all meta analyses, indicating that despite methodological and clinical differences, the main findings seems to be robust.

Limitation

- The studies in this review used a number of different methods to collect and analyse the microbiota samples.
- The number and composition of CST differed between the studies especially the non Lactobacillus -dominated CSTs.
- The research area is fairly new and has not yet reached consensus on the preferred categories and method.

Metformin Plus Megesterol Acetate Compared with Megesterol Acetate Alone as Fertility Sparing Treatment in Patients with Atypical Endometrial Hyperplasia and Well Differentiated Endometrial Cancer: A randomised controlled trial

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Abstract

Introduction: Progestin therapy is widely accepted as the main fertility sparing treatment in young women with atypical endometrial hyperplasia [AEH] and well differenciated endometrial cancer [EEC]. However, 20-30% of these patients still fail to achieve complete response [CR] and loose fertility after hysterectomy. Prolonged treatment period and higher doses also weaken patients compliance and increases side effects.

Clinical research supports use of metformin in the fertility-sparing treatment for AEH and EEC patients. Metformin suppresses the growth of breast, ovarian, prostate and endometrial cancer cells via altering glucose metabolism and inhibiting the P13K-AKT-mTOR signalling pathway. Metformin also increases the expression of the progesterone receptor and sensitise the progestin resistant endometrial cancer cells to medroxyprogesterone induced apoptosis. Latest meta-analysis also shows metformin synergise with progestin by reversing the AEH to normal endometrial histology, reduces cancer progression biomarkers and improving overall survival of EC patients.

Objective: To assess the efficacy of metformin in megesterol acetate [MA] based fertility sparing treatment for patients with atypical endometrial hyperplasia and endometroid endometrial carcinoma.

Design: A randomised, single centre, open label, controlled trial conducted between October 2013 to December 2017.

Setting: Shanghai OBGYN hospital of Fudan University, China.

Population: A total of 150 patients [18-45 years old] with primary AEH or well differenciated EEC were randomised into an MA group [n=74] and an MA plus metformin group [n= 76]

Methods: Patients with AEH or EEC were firstly stratified, then randomised to receive MA [160mg orally daily] or MA [160mg orally daily] plus metformin [500 mg orally three times a day].

Main Outcomes and Measures: The primary efficacy parameter was the cumulative complete response

[CR] rate within 16 weeks of the treatment [16w-CR rate]; the secondary efficacy parameters were 30w-CR rate and adverse events.

Results: The 16w-CR rate was higher in the metformin plus MA group than in the MA only group [34.3 versus 20.7%, odds ratio [OR] 2.0, 95% confidence interval [CI] 0.89-4.51, P=0.09] but the difference was more significant in 102 AEH patients [39.6versus 20.4%, OR 2.56, 95% CI 1.06-6.21, P= 0.04]. This effect of metformin was also significant in non-obese individuals [51.4 5 versus 24.3%, OR 3.28,95% CI 1.22-8.84 P= 0.02] and insulin sensitive [54.8 versus 28.6%, OR 3.04, 95% CI 1.03-8.97, P=0.04%] subgroups of AEH patients. No significant results were found in secondary endpoints.

Conclusions: As fertility-sparing treatment, metformin plus MA was associated with a higher early CR rate compared with MA alone in AEH patients.

Strength

- Prospective randomised controlled trial with large sample size[150 patients]
- Result also showed the efficacy of metformin in AEH patients without obesity, hypertension or diabetes in Chinese population.

Limitations

- It was a single centre phase 2 trial, with a relatively smaller sample size of EEC participants.
- The lack of double blinding design and placebo were also a weakness.
- Hysteroscopies got delayed for few patients for 2-4 weeks which were scheduled for all patients at every 3 months as it was a single centre study and many patients were from other cities and also some developed vaginitis or due to conflict with their working hours.
- Lack of sufficient cases for statistical analysis could generate bias and might be the reason why the difference between two treatments failed to achieve statistical significance.

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Laparoscopic Ovarian Salvage and Oophoropexy in Adnexal Torsion

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Adnexal torsion Was first described in 1891 . It is the fifth commonest gynaecological emergency .It has a prevalence of 2.5 to 7.4%.

It can occur in all age groups including children.

Predisposing factors are the presence of ovarian cyst/ Mass, hyper stimulated ovaries, pregnancy, sub-fertility treatment etc.

Recurrence rate is 10%

The condition is primarily diagnosed by history and high index of suspicion.

Conservative management of adnexal torsion viz detorsion cystectomy, Oophoropexy excision of torsed adnexa -salpingo opherectomy laparoscopically was studied in 27 Patient at Sir Ganga Ram Hospital over a period of five years from January 2015 to December 2020.

There is a lack of correlation between onset of symptoms and onset of overian ischaemia but better surgical outcome is seen in early surgical intervention.

Oophoropexy is a good surgical modality to prevent adnexal torsion, recurrence.

We have combined ovarian ligament plication with fixing of inferior pole of ovary which retains anatomy and therefore does not affect fertility issues

The management of adnexal torsion must be individualised to fit safety and preventative parameters.

Ovarian rescue can be carried out despite late presentation, laparoscopically preserving anatomy and fertility.

A Case of Esophageal Carcinoma with Pulmonary Metastasis with Pregnancy

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Introduction: Esophageal cancer is one of the leading cause of cancer-related death worldwide. The complete resection of esophageal cancer tissue with surrounding malignant lymph nodes is the sole potential curative treatment. Preoperative staging is very important to determine the appropriate treatment modalities for patient. Computed tomography is the first advised imaging technique for the evaluation of extent of disease and/or staging after the pathologic examination. Esophageal cancer is seen very rarely during pregnancy. The incidence of esophageal carcinoma ranges from 0.07 to 0.1% of all malignant neoplasms. The symptoms are usually misinterpreted as pregnancy related symptoms.

Case: We report here a case of 28 year old G3P1L1A1 presented to casualty at 36+5 weeks gestation, h/o previous cesarean section with complaints of haemoptysis, malena and dysphagia, cough since last one month and now aggravated for 4 days, along with history of weight loss.

Patient had undergone emergency cesarean section under spinal anesthesia and delivered a female baby of 2.180 kgs. She was evaluated postoperatively. Gastroenterology opinion was taken, advised upper GI endoscopy, HRCT thorax. Large esophageal growth seen, likely metastatic. Esophageal biopsy confirmed well differentiated squamous cell carcinoma.

Medical oncologist opinion sought and she was planned for palliative chemotherapy after 3 weeks of caesarean section in view of advanced stage esophageal cancer with lung metastasis.

She took discharge on request to complete her rest of the treatment from Government Medical

College and Hospital. On telephonic follow up, she was planned for 6cycles chemotherapy and feeding Jejunostomy. She received 3 cycles Chemotherapy with Carboplatin and Paclitaxel till now.

Conclusion: Gastrointestinal complaints during pregnancy should be looked at suspiciously and especially in persistent cases, as in present scenario. Malignancy should be kept in mind and further investigations should be performed.

Post Menopausal Women with Cervicovaginal Agenesis with Rare Form of Mesenchymal-Epithelial Tumor

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Case 2: A 46 yrs. Old P0L0 post-menopausal woman came to gynae OPD with complains of low backache and pain in lower abdomen off & on for 4 months and frequency of micturition for past 15-20 days. Patient was diagnosed with cervicovaginal atresia at 16 yrs. of age as she had primary amenorrhea and cyclical abdominal pain since the age of 14 yrs. and she underwent multiple laparotomies and vaginal reconstruction surgeries followed by vaginal moulds after which she resumed her menses but required multiple hospital visits for dilatation procedures and menstrual difficulty and finally at 38 yrs. of age her menses stopped completely and she was declared to have attained menopause by her doctor and she did not come for gynae check-up after that. On examination, her vitals were normal, general examination was normal, P/A soft, multiple scares of Laparotomy were present, P/S: blind vagina of 6-7 cm length, P/R uterus was 6 weeks size: USG and MRI revealed hematometra with 4x4 cm growth arising from fundus and right lateral wall of uterus with breach is endometrial- myometrial junction on right side suggestive of malignant growth ? Endometroid endometrial carcinoma. No lymph nodes, no parametrial involvement were noted. On investigation, CA 125 was 56.50, FSH 97.50 E2 was 20. Rest all were normal.

Since hysteroscopy & D&C was not possible in her case so patient was planned for EUA with total laparoscopic hysterectomy with B/L salpingo-oophorectomy & proceed. Intra- operatively dense adhesions were encountered between omentum and anterior abdominal wall, bowel and lateral pelvic wall & uterus was also covered with dense bowel adhesions which were released & total Laparoscopic hysterectomy with B/L salpingo-oophorectomy & specimen was retrieved by mini-laparotomy. Cut section revealed mulberry like growth 4x4 cm arising from fundus & right lateral wall of uterus & specimen was sent for frozen section which revealed malignant mixed mullerian tumor. B/L pelvic lymph node sampling was done. Final HPE reported biphasic tumor with epithelial and mesenchymal component and cystic mucoid elements. Epithelial component was benign & sarcomatous mesenchymal part with ki 67 activity of 4-5% & negative for CO-10 S/O low grade uterine adenosarcoma and all lymph nodes were negative for tumour cells. Medical Oncologist and Oncosurgeon opinion were taken and advised that no treatment was required.

Discussion: Uterine adenosarcoma was first described by Crement and Scully in 1974. These tumours are very rare and constitutes 5% of uterine sarcomas. These tumour are of low malignant potential. They are biphasic tumour composed of malignant mesenchymal and benign epithelium. The epithelial is usually of endometrium like cells but may also resemble secretory, squamous, clear or mucinous cells. If sarcomatous part occupies >25% of the tumour volume it is refrred as sarcomatous overgrowth (<10% cases). It is associated with a risk of recurrence and has poor prognosis. Treatment is hysterectomy without morcellation. Role of B/L pelvic &paraaorticlymphadenectomy is not clear as lymph node involvement is 3-4%.

In this case, it is important to emphasize the role of annual screening after menopause, also as she had cervico-vaginal agenesis & she stopped bleeding at 36 yrs. of age and she was unaware of the fect that she developed haematometra& an uterine growth which was diagnosed after 8 years.

Case of Endometrial Carcinoma – Atypical metastasis

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Mrs. Xy, 51yrs old P_2L_2 with previous one LSCS, consulted us in January 2020 with history of

prolonged & heavy periods since 3-4 months. USG done outside, report showed uterus 56 X 47 X 56 mm with small fibroid seedling & ET was 17.4 mm, both ovaries were normal. Her previous menstrual cycles were regular with moderate flow.

Her General physical examination was normal. On per abdomen examination, a 5x6 cm soft cystic mass felt in abdominal wall about 2-3 cm below umbilicus on left side, otherwise there was no organomegaly.

On per vaginal examination uterus was bulky, retroverted, mobile & both fornices were free & above mentioned mass was not felt. LBC report showed AGUS (atypical glandular cells of underdetermined significance), rest all reports were normal.

She underwent D & C hysteroscopy in view of AGUS on LBC & increased endometrial thickness. HPE showed complex atypical hyperplasia with foci of well differentiated adeno-carcinoma. Her Ca-125 was 10 units per ml & MRI whole abdomen reported-heterogenous signal intensity mass lesion in left abdomen extending to pelvic cavity of size 70 x 52x 57 mm. left ovary was not made out separately, right ovary was normal. Irregular thickening of junctional zone & enlarged common & internal iliac LN were reported.

True cut biopsy of abdominal wall mass was reported as metastatic adeno-carcinoma with focal squamous differentiation likely primary from genital tract, possibly endometrium. PET CT showed FDG avid soft tissue mass lesion on left side of abdominal cavity abutting left parietal wall of size 5x7x5.2 cm.

She was planned for radical hysterectomy & excision of parietal mass after pre op work up & written consent. On per op – there was 5x6 cm mass adherent to parietal peritoneum and posterior rectal sheath, adherent to omentum, bowel loops & left adnexa, same separated & mass was excised. Total hysterectomy with BSO with B/L pelvic lymphadnectomy was done & specimen was sent for HPE. On cut section small tumour was seen at fundus with no obvious myometrial invasion.

Final histopathology report was as - endometrioid carcinoma with squamoid differentiation grade II, myometrial invasion less than 50%. Uterine serosa, cervix, cervical stroma, tubes, ovaries, bilateral parametrium, omentum & lymphovasular space were free of lesion

- Two out of 6 left pelvic LN showed metastasis
- Right side lymph nodes were free of tumour
- Left parietal mass was metastatic carcinoma same as the uterus.
- IHC tumour cells in endometrium with patchy ER & PR & negative for Napsin A
- Cytology was negative
- Pathological staging PTNM – PT_1A, PN_1A, M_1
- FIGO staging IV B, T_1A, N_1M_1

She received seven cycles of paclitaxel & carboplatin every 3 weeks after surgery, chemotheraphy was followed by external, radiotherapy & brachytherapy.

Discussion: Endometrial Cancer is most common Gynae malignancy in developed countries & second most common in developing countries. Typical sites for metastasis are pelvic, para aortic lymphnodes, vagina, peritoneum & lungs. Atypical sites include abdominal wall & muscle (2-6%), extra abdominal nodes (0.4-1%) spleen (1%), brain (less than 1%) very rare but metastasis have been reported in pancrease, adrenal & appendix also in literature. Majority of reported cases were recurrences after completion of primary treatment. Only a small subset of case reports have shown atypical metastasis with naïve stage III or IV stage.

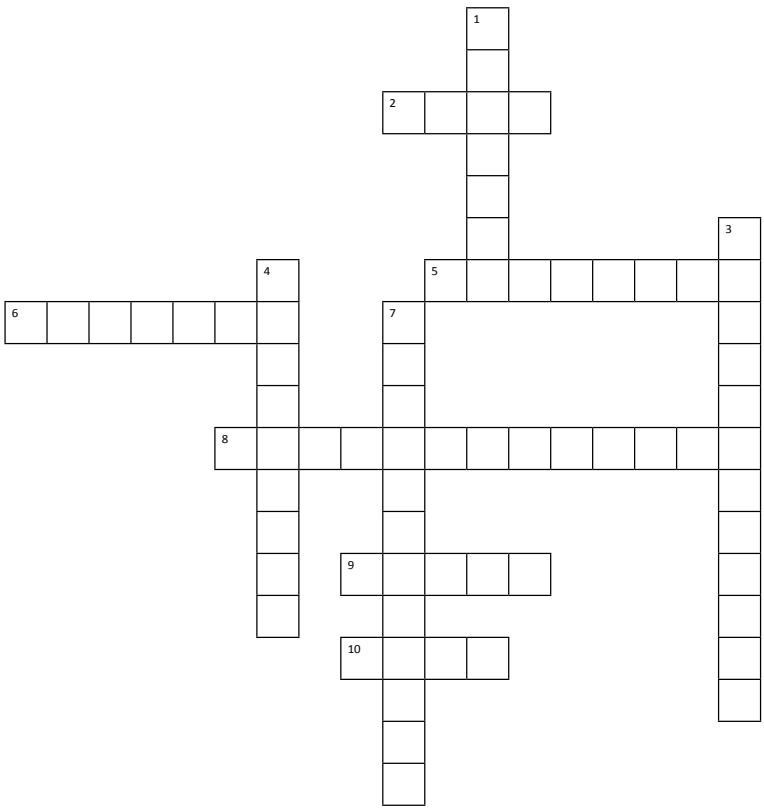
Treatment of metastatic endometrial cancer includes complete surgical excision of lesion followed by chemotheraphy (Paclitaxel & carboplatin). Radiotherapy is indicated for naïve disease on in cases where patient has not received previously. Monitoring should be done after every 2-3 cycles with whole abd CT & Ca -125 levels. Endocrine therapy with megestrol acetate alternate with tamoxifene should be considered wherever it is indicated.

Cross Word Puzzle

Ruma Satwik
Consultant, Centre of IVF and Human Reproduction, Sir Gangaram Hospital, New Delhi

CROSSWORD

Test your knowledge of Reproductive Anatomy and Physiology



Across

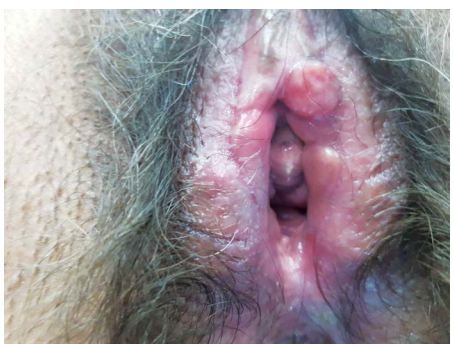
2. The procedure involving removal of watchman lymph node. (abbreviation) (4)
5. 70--90-70 is a strategy to accelerate elimination of____ cancer (8)
6. Origin of a large proportion of high grade serous carcinoma of ovary (7)
8. Primary colonizing bacteria of a healthy vagina (13)
9. Smooth muscle tumour that cannot be unequivocally categorized as benign or malignant (5)
10. Percentage of endometrial cancer found in women younger than 40 years(4)

Down

1. A Contrast agent used in contrast enhanced ultrasound (7)
3. Process of studying micrometastases by taking multiple thin sections and subjecting this to histopathology & immunochemistry
4. Name of the nonavalent HPV vaccine (8,1)
7. The most frequent type of endometrial cancer (12)

PICTORIAL QUIZ

Sharmistha Garg
Associate Consultant, Sir Ganga Ram Hospital, New Delhi



Questions

Q 1. Identify the lesion?

Q 2. What are the HPV subtypes related to this lesion?

Q 3. Where are the sentinal nodes for this lesion located?

Announcement

Calendar of
Virtual Monthly Clinical Meetings 2020-21

29th May, 2020	B L Kapoor Hospital
26th June, 2020	VMMC & Safdarjung Hospital
31st July, 2020	AIIMS
14th August,2020	Lady Hardinge Medical College
28th August, 2020	Army Hospital- Research & Referral
11th September,2020	Apollo Hospital
25th September, 2020	DDU Hospital
23rd October to 6th November, 2020	AOGD Annual Conference Activities
27th November, 2020	MAMC & LNJP Hospital
18th December, 2020	Sir Ganga Ram Hospital
1st January, 2020	ESI Hospital
29th January, 2021	Dr RML Hospital
26th February, 2021	UCMS & GTB Hospital
26th March, 2021	Lady Hardinge Medical College
23rd April, 2021	Apollo Hospital

Answer: January 2021 Issue

Crossword

Across

2. SLNB
5. Cervical
6. Fimbria
8. Lactobacillus
9. Stump
10. Five

Down

1. Sonovue
3. Ulrastaging
4. Gardasil 9
7. Endometrioid

Pictorial Quiz Answers

A 1. Squamous cell carcinoma vulva

A 2. HPV - 16, 18 and 33

A 3. Superficial inguinal femoral nodes on left side just medial or over the femoral vessels.

Important Announcement

Gurukul classes will be held w.e.f 5th to 7th February, 2021 under the aegis of AOGD & ISOPARB, organized by Institute of Obstetrics & Gynaecology, Sir Ganga ram Hospital.

Gurukul will include case discussions, Table vivas and OSCE.

Registration is complimentary but mandatory
Click here for registration

In case of any problem regarding registration kindly contact

Mr Vinod, 98913304156 or **Mr Dharmendra,** 9873784412

AOGD Events Held

On 10th December 2020, a webinar **"THE TALK- FAQs on Ovarian Cyst"** was conducted under the aegis of AOGD.

On 12th December 2020, a webinar on **"Mastering the art of difficult obstetric manoeuvre: Breech, Shoulder Dystocia & fetal extraction during Cesarean Delivery"** by Department of Obstetrics & Gynaecology, UCMS & GTB Hospital, New Delhi was conducted under the aegis of AOGD.

On 17th December 2020, a webinar on **"Diagnosis and Management of GDM and Approach to Breast Lump"** was held under the aegis of DGF North Multidisciplinary Committee of AOGD & Breast Committee of FOGSI.

On 18th December 2020, **"AOGD Monthly Meeting"** was organized by Sir Ganga Ram Hospital, New Delhi.

On 20th December 2020, a webinar **"22nd Gynae Update"** was organized by IMA Janakpuri under the aegis of AOGD.

On 20th December 2020, **"International Webinar: Endoscopy Updates"** was organized by Endoscopy Committee AOGD & Global Community of Hysteroscopy.

On 26th December 2020, a webinar on **"11-14 weeks (Screening Strategies)"** was organized by FOGsd with FOGSI, AOGD, NARCHI Delhi, IFS-EP-SIG and Sonoschool.

On 1st January 2021, **"AOGD Monthly Clinical Meeting"** was held by ESIC PGIMSR Basaidarapur Hospital, New Delhi.

On 4th January 2021, a webinar on **"Vulvovaginitis"** was held under the aegis of Multidisciplinary Committee of AOGD.

On 5th January 2021, a webinar on **"AdeSabharwal"** was held under the banner of AOGD Endoscopy Committee.

On 6th January 2021, a webinar by Dr. Anita Sabharwal was held under the aegis of AOGD.

Forthcoming Events

On 14th January 2021, a webinar **"FAQ on Endometriosis"** will be held under the aegis of AOGD.

On 15th January 2021, a webinar **"FAQ on AUB"** will be held under the aegis of AOGD.

On 16th January 2021, a webinar **"FAQ on Breast Cancer"** will be conducted under the aegis of AOGD.

On 18th January 2021, a webinar **"FAQ on Small Babies"** will be held under the aegis of AOGD.

On 23rd January 2021, CME on **"Cervical Cancer Prevention"** will be held under the aegis of AOGD.

On 1st February 2021, a webinar **"FAQ on GDM"** will be held under the aegis of AOGD.

On 17th February 2021, a webinar **"FAQ on Uterine Fibroid"** will be held under the aegis of AOGD.

AOGD Sub Committee Nomination (2021-23)

Nominations are invited for the post of chairperson of the following sub-committees for the year 2021-23

1. Urogynecology committee
2. Endoscopy Committee
3. Adolescent Committee
4. Safe Motherhood Committee
5. Fetal Medicine and Genetics committee
6. Oncology Committee
7. Reproductive Endocrinology Committee
8. Endometriosis committee
9. QI Obst & Gynae Practice committee

Eligibility Criteria

1. Person should be a member of AOGD and have at least 10 years standing in the profession with at least 5 years duration of holding senior position in the respective institutions.
2. Chairperson of a subcommittee has to be a member of any subcommittee earlier for at least 1 year.
3. No repeat nomination will be considered after one term of two years.
4. In case of two people applying for the same post, the decision of the executive committee will be final.
5. In case of any deviation, the decision would be taken by executive committee.
6. Two posts cannot be held by any member at one particular time.

Please send the nominations by email on secretaryaogdsgrh2020@gmail.com

Or

By post, the nominations on plain paper should reach: Gynae Office, Institute of Obstetrics and Gynecology, Sir Ganga Ram Hospital, Sarhadi Gandhi Marg, Old Rajinder Nagar, New Delhi-110060 by 31st January, 2021 along with bio-data stating the eligibility.