CME MODULE

ON GYNAECOLOGICAL CANCERS FOR PHMS DOCTORS

STATE INSTITUTE OF HEALTH AND FAMILY WELFARE, UTTAR PRADESH
In Association with Genital Cancer Control Unit, King George's Medical University, Lucknow

AKNOWLEDGEMENTS

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Processed and Realization

MESSAGE

Shri Brajesh Pathak

Hon'ble Deputy Chief Minister
Hon'ble Minister of
Medical Health and Family Welfare
Department
Government of Uttar Pradesh

Fast changing medical science and research makes in mandatory for doctors to attend continued medical education programme so that they remain well abreast with the recent developments is medical science. This is not only necessary to enhance the knowledge of clinicians but to extend its benefit to their patients too.

Inching towards the 3As (affordability, accessibility, and availability) healthcare goal spelled out by the government, and further accelerated by the COVID-19 pandemic, the Government of Uttar Pradesh in its efforts to improve its Healthcare Ecosystem, intends to make giant strides through Continuing Medical Education (CME) by incorporating technological and medical advances.

PHCs/CHCs serves as a first port of call to a qualified doctor in the public health sector and though these CME programmes recent knowledge and skills will be imparted to Medical Officers in systematic manner to update the existing proficiency of Medical Officers. This will definitely improve the patient care, patient confidence and patient satisfaction.

In lieu of the above the State Institute of Health & Family Welfare (SIHFW), has started developing Modules for Continuing Medical Education (CME) which are need of the hour required to our health personnel. I hope that this module on Continuing Medical Education (CME) on Gynecological Cancers for Medical Officers in Provincial Health & Medical Services in Uttar Pradesh, is the first of many to come, that will aid our Medical Officers in knowledge up gradation on concurrent intervention practices.

I wish the faculties at State Institute of Health and Family Welfare (SIHFW), Lucknow, Uttar Pradesh that they should continue developing such module on Continuing Medical Education (CME) for the benefit of Medical Officers in Provincial Health & Medical Services in Uttar Pradesh that will ultimately benefit their patients too.

(Brijesh Pathak)


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MESSAGE

Shri Mayankeshwar Sharan Singh

Hon'ble State Minister
Medical Health and Family Welfare Department
Government of Uttar Pradesh

I am proud of the fact that the SIHFW through this module on Continuing Medical Education (CME) on Gynecological Cancers for Medical Officers in Provincial Health & Medical Services in Uttar Pradesh, is addressing the need of knowledge up gradation in management and treatment of Gynecological Cancers.

Ovarian and cervical cancers are the most common gynecological cancers affecting women worldwide and in India. Cervical cancer is on a declining trend, but remains the second most common cancer in women after breast cancer.

This module on CME on Gynecological Cancers intents to facilitates our Medical Officers to address the issue of treatment and management of Gynecological Cancers and in turn improve the health of the beneficiaries.

It is most important fact that to achieve the desired goals and objectives of the Department of Health and Family Welfare, we must have highly qualified trained and dedicated human resource to look after the family welfare services with best of their capabilities. This module on Continuing Medical Education (CME) on Gynecological Cancers will definitely serve a similar goal.

I wish the faculties at State Institute of Health and Family Welfare (SIHFW), Lucknow, Uttar Pradesh success in their endeavors of aiding an improved health service delivery system through such Continuing Medical Education on Gynecological Cancers.

(Mayankeshwar Sharan Singh)


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FOREWARD

Shri Partha Sarthi Sen Sharma

Principal Secretary
Department of
Medical Health and Family Welfare
Government of Uttar Pradesh

The purpose of this module on Continuing Medical Education (CME) on Gynecological Cancers for Medical Officers in Provincial Health & Medical Services in Uttar Pradesh is to develop, increase and maintain the knowledge, competence, and professional performance and relationships that a Medical Officer uses to provide services for patients, the public and the profession.

Through this module the Medical Officers will be provided with opportunities to update knowledge, skills and practices on Gynecological Cancers screening and treatment besides critical care, service delivery and infection control.

This will definitely improve the patient care, patient confidence and patient satisfaction and will provide an opportunity to enhance State's healthcare ecosystem by delivering healthcare services to the person at the very end of the system.

This module is developed in recognition of the fact that health and welfare programmes needs to keep up with the recent development in the field of healthcare and biomedical research.

While the Uttar Pradesh healthcare space remains abuzz with authenticity, research, ethics and interventions in CME delivery, the larger impact of this CME on Gynecological Cancers on the populace can only be measured in the times to come.

I would like to take this opportunity to congratulate State Institute of Health and Family Welfare (SIHFW), Lucknow, Uttar Pradesh and other subject matter experts in developing this important CME module on Gynecological Cancers. I hope SIHFW will come up with other subject centric CME modules to facilitate the transition of state's health care delivery mechanism.

(Partha Sarthi Sen Sharma


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MESSAGE

Dr. Renu Srivastava Varma
Director General
Department of
Medical Health and Family Welfare
Government of Uttar Pradesh

Gynecological cancers are among the most common cancers in women and hence an important public health issue. Due to the lack of cancer awareness, variable pathology, and limited access to proper screening facilities, most women report at advanced stages thus adversely affecting the prognosis and clinical outcomes. Ovarian cancer has emerged as one of the most common malignancies affecting women in India and has shown an increase in the incidence rates over the years.

Through this module on Continuing Medical Education (CME) on Gynecological Cancers for Medical Officers in Provincial Health & Medical Services in Uttar Pradesh, State Institute of Health & Family Welfare has developed a comprehensive CMEs detailing out steps in critical care, service delivery, patient safety, quality management, infection control, and up gradation in knowledge delivery which will help in early screening, detection and treatment of Malignant neoplasms.

I hope that after this CME, Medical Officers in Uttar Pradesh will be able to scale up the service delivery in provide screening, management, referral and treatment in their health facilities, thus benefitting communities, in addition to improving clinical and technical area of expertise resulting in improved access to health services and enhancing patient satisfaction and population health.

With the development of this module on Continuing Medical Education (CME) on Gynecological Cancers for Medical Officers in Provincial Health & Medical Services in Uttar Pradesh, State Institute of Health & Family Welfare has established genuine links between the theory and practice of healthcare management. I wish the faculties at State Institute of Health and Family Welfare (SIHFW), Lucknow, Uttar Pradesh the best and hope that many such customized CME modules will be published in the near future.

(Dr. Renu Srivastava Varma)


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MESSAGE

Dr. Anita Joshi

Director General Family Welfare
Directorate of Family Welfare
Government of Uttar Pradesh

This module on Continuing Medical Education (CME) on Gynecological Cancers for Medical Officers in Provincial Health & Medical Services in Uttar Pradesh is intended to target even those Medical Officers who are posted at CHCs/PHCs. This module will heighten the importance on the role of the Medical Officers at CHCs/PHCs in screening, prevention and treatment of Gynecological Cancers, and review public health services in the districts accordingly.

By collating the relevant information in the field of gynecologic oncology, covering all domains such as basic sciences, preventive oncology, pathology, radiological imaging, clinical outcomes and providing case studies to illustrate best practice, the module seeks to be a working document which can also be reviewed and updated periodically based on the experience of the implementation of the public health services.

I am especially pleased to note that although CMEs in Uttar Pradesh healthcare ecosystem are still in its nascent stage but such developments will lead the way forward in creating tailored CMEs for critical care, service delivery, patient safety, quality management, infection control, and authentic knowledge delivery.

It is vital to introduce CMEs combining video and live demonstrations along with simulation-based skill modules and rigorous assessments led by experts in order to measure further impact.

I congratulate the faculties at State Institute of Health and Family Welfare (SIHFW), Lucknow, Uttar Pradesh in developing this convergent module along with experts from the field of Medicine. This module addresses the need to have a holistic view on public health by also discussing other relevant guidelines and policies that seek to public health service delivery system in the guidebook.

(Dr. Anita Joshi)


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MESSAGE

Dr. Deepa Tyagi

Director General (Training)
Medical, Health & Family Welfare
Government of Uttar Pradesh

This module on Continuing Medical Education (CME) on Gynecological Cancers for Medical Officers in Provincial Health & Medical Services in Uttar Pradesh provides a comprehensive, coherent and research-based insight to treatment of various Gynecological Cancers. It has been designed and written for Medical Officers and healthcare professionals and takes government perspective in consideration, drawing on and comparing ideas and developments from national and international health care practices.

The module is structured in such a manner that it covers in the field of gynecologic oncology, covering all domains such as basic sciences, preventive oncology, pathology, radiological imaging, and clinical outcomes in the context of public health and providing an overview of about future development and trends in Gynecological Cancers treatment.

Faculties at State Institute of Health and Family Welfare (SIHFW), Lucknow, Uttar Pradesh has done a commendable job by publishing this module on Continuing Medical Education (CME) on Gynecological Cancers for Medical Officers in Provincial Health & Medical Services in Uttar Pradesh. I hope the participants coming to attend their upcoming CME will take advantage of this initiative and make the most in their field with this handy module.

(Dr. Deepa Tyagi)


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ACKNOWLEDGEMENT

Dr. Rajaganapathy R.
Director
State institute of
Health & Family Welfare
Government of Uttar Pradesh

Development in medical science and research compels doctors to stay up to date current practices and trends. It is widely felt that CME programmes are earnestly needed to impart recent knowledge and skills in systematic manner to update the existing proficiency of doctors.

For the benefit of Medical Officers in Health & Medical Services in Uttar Pradesh and with the objective to enhance patient care, patient confidence and patient satisfaction, State Institute of Health & Family Welfare with the help of subject matter experts has developed a module on Continuing Medical Education (CME) on Gynecological Cancers for Medical Officers in Provincial Health & Medical Services in Uttar Pradesh.

This module on CME on Gynecological Cancers has laid emphasis on convergent approach of screening, diagnosing, managing and treatment of malignant neoplasms. The purpose of developing this module is to facilitate learning among Medical Officers so that their practices may reflect the best medical care for their patients. .

I would like to congratulate the faculties of State Institute of Health and Family Welfare (SIHFW), Lucknow, Uttar Pradesh and senior faculties of Queen Mary's Hospital, King George's Medical University, Lucknow, Uttar Pradesh in conceiving and giving action to shape though this Module.

This is only one step in the effort to support and enhance the quality of service delivery though knowledge and skill enhancement of Medical Officers. Many more subject centric and customized CME modules will be developed and published in the near future.

(Dr. Rajaganapathy. R)


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Section

1

Cervical Cancer

1. Cervical Cancer Screening
2. Diagnosis and Treatment of CIN
3. HPV Vaccination
4. Clinical Features, Diagnosis and Staging of Cervical Cancer
5. Treatment Modalities for Cervical Cancer


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Author: Prof. Nisha Singh

Introduction

The worldwide incidence of cervical cancer is approximately 510,000 new cases annually, with 288,000 deaths worldwide. This is the most common gynaecological cancer in India, and second most common in women after breast cancer.

It is estimated that in India there are around 132,000 new cases and 74,000 deaths per year accounting to nearly one-third of global cervical cancer deaths. Indian women face a 2.5% cumulative lifetime risk and 1.4% cumulative death risk from cervical cancer. It is now an established fact that human papilloma virus (HPV) infection is the primary cause of cervical cancer. The prevalence of HPV infection in general population at a given time is 6.6%.

There has been decline in the incidence and mortality due to cervical cancer mainly because of better screening modalities with efficient utilisation. Screening leads to early detection and treatment of pre invasive lesions of cervix, which when left untreated for 10 to 20 years, can lead to cervical cancer. The precursor lesions of cervix leading to cervical cancer are together called Cervical Intraepithelial Neoplasia (CIN).

The importance of early identification and prompt treatment of CIN cannot be overemphasized when we know that duration of pre invasive lesion and severity of dysplasia clearly connotes the neoplastic potential of the cervical lesion.

Histology of Cervix

The endocervix is covered by columnar epithelium (single layer of tall column shaped cells with elongated basal nucleus), while the ectocervix is covered by squamous epithelium (multiple layers of flat cells).

The junction between these two types epithelium is called Squamocolumnar Junction (SCJ). It is a dynamic junction that responds to physiological hormonal changes during puberty, pregnancy, menopause and also to external hormones like estrogen replacement therapy.

The SCJ is called dynamic because it keeps changing its position due to metaplastic transformation of columnar cells to squamous cells during reproductive years. This metaplasia is also the reason behind formation of the Transformation zone.

The original SCJ present at birth is an abrupt junction between the squamous epithelium of the ectocervix and the columnar epithelium of the endocervix.

Through exposure to estrogen (at birth, during puberty, and throughout reproductive life), the glycogen in the exfoliated cells of the vagina is converted into lactic acid, accounting for the acidity of the vaginal secretions (pH 4.5).

The acidity, along with other factors, stimulates the replacement of the columnar epithelium with squamous epithelium, thereby forming the New SCJ. The area between the original SCJ and the new SCJ is known as the transformation zone (TZ).

Etiopathogenesis of Cervical Cancer

Cervical cancer and CIN are caused by Human Papilloma Virus (HPV) infection in majority of cases. HPV is a non enveloped double stranded DNA virus, transmitted through sexual contact. More than 150 strains of HPV are known till now and 30 of them are anogenital type. High risk lesions are mostly caused by HPV types 16, 18, 31, 33, 35, 39, 45, 51 and 58.

HPV 16 (54%) and 18 (13%) account for majority of cervical cancer cases. HPV 16 also causes other anogenital (vulval, vaginal, anal) and oropharyngeal cancer. Low risk HPV type like 6, 11, 40 and 42 are not oncogenic but 6 and 11 causes most of the genital warts.

Most of the sexually active reproductive age women acquire HPV infection once in lifetime but also clear it through natural process. About 20% have persistent HPV infection that can later convert into CIN or cervical cancer. The risk factors for persistent HPV infection are low socioeconomic status, poor menstrual hygiene, nutritional deficiencies, poor immunity, early age at first intercourse, multiple sexual partners, reproductive tract infections, ethnicity (Asian, African), multi parity, smoking and oral contraceptive usage.

WHO Call for Elimination

In 2020, the World Health Organization (WHO) announced and then launched the strategy for cervical cancer elimination by 2030. According to WHO, cervical cancer can be eliminated if:

90% of eligible candidates are fully vaccinated against HPV.

70% of women are screened by high performance tests by 35-45 years of age.

90% of women with CIN or cervical cancer are treated.

Cervical Cancer Screening

Screening for cervical cancer aims at detecting and treating the precursor (CIN). This is the best example of secondary prevention and a strong pillar for the WHO goal of elimination of cervical cancer by the year 2030. The three main screening modalities are HPV DNA testing, Cytology and VIA

HPV DNA Test

Screening frequency by using HPV testing is as low as 5 yearly, as this method has very high sensitivity and negative predictive value. In India, these tests are available only in good resource settings.

Sample collection is performed with a specially designed brush and then placed in liquid transport medium. Sample is sent to the laboratory at room temperature. Self collected sample can also be used for HPV testing. Both DNA or RNA based tests are available. DNA Tests include Direct genome detection, amplification of viral DNA fragment using PCR amplification and genotyping of HPV-16 and18. RNA TESTS include amplification of E6/E7 proteins or monoclonal antibodies

Cervical Cytology

PAP SMEAR - Pap smear sample should be taken from transformation zone after proper visualization of cervix by using cusco's self retaining speculum or Sim's speculum with anterior vaginal wall retractor. Ayer's wooden spatula has two ends, a handle and an asymmetrical heart shaped business end. Keeping the longer part of business end fixed on endocervical canal, the shorter part is rotated for 360 degree. The endocervical / cytobrush is used to obtain endocervical sample, by inserting and rotating it in endocervical canal. The Ayer's spatula sample taken is smeared on two-third of the glass side, endocervical sample spread on the remaining area. For quickly fixing the slide, it should be immersed in pap jar containing 1:1 solution of 95% ethyl alcohol and ether or fixative spray can also be used. The pap jar is then sent for cytological examination.

Being a simple test, it is easy to learn and does not require much training but laboratory support and cytologist are required for evaluation of slides and reporting takes quite some time. The specificity of pap smear is very high (98%) but its sensitivity is as low as 50%. There could be sampling and interpretation errors.

Liquid Based Cytology (LBC) - Liquid based medium is used to collect and preserve the cervical sample. LBC removes any artifacts, allows better cytological assessment of basal, parabasal and superficial cells and the sample can also be used for HPV testing. It is comparatively expensive and requires better infrastructure

and laboratories. Cytology results are reported as per the Bethesda system revised in 2014. The reporting includes specimen adequacy, interpretations about squamous lesions (ASCUS, LSIL. ASC-H, HSIL, SCC) and glandular abnormalities (AGC, endocervical adenocarcinoma) in addition to infections and reactive cellular changes.

VIA (Visual Inspection with Acetic Acid)

Acetic acid application on cervix causes precipitation and coagulation of cell protein changing the normal transparent filter into opaque epithelium. The reflected light from the opaque epithelium gives a white color to the epithelium. Neoplastic epithelium has a high protein content because of large nuclei, extra chromatin, and intact cytoplasm. The higher is the grade of neoplasia, the greater is the protein content and the greater is the density of acetowhitening. 5 ml of Glacial acetic acid is mixed with 95 ml distilled water to make 5% solution which is used for VIA test. Acetic acid should be applied for one complete minute. Unused acetic acid should be discarded at the end of the day.

VILI (Visual Inspection with Lugol's Iodine

Iodine is glycophilic and stains mahogany brown or black. Squamous epithelial cells are glycogen rich whereas there is little or no glycogen in precancerous lesions and invasive cancer cells. Columnar epithelial cells lack glycogen hence there is no iodine uptake by these cells. Immature metaplasia and inflammatory lesions are partially glycogenated and when stained appear as

scattered, ill defined uptake area. Precancerous lesions and invasive cancer do not take up iodine (as they lack glycogen) and appear as well defined , thick, mustard or saffron yellow area. Lugol's iodine can be prepared with 10gram of Potassium iodide mixed with 5gram of Iodine crystals and 100 ml of distilled water or boiled water at room temperature. It can be stored for one month in a dark coloured bottle as 5% Lugol's iodine solution.

Guidelines for Cervical Cancer Screening

WHO guidelines (2021) for cervical cancer screening include 23 recommendations and 7 good clinical practice statements. The major change has been the recommendation for using HPV DNA test as the primary screening modality in view of the difficulty in maintaining quality assurance with other screening methods. HPV DNA test should be used for screening all women in general population between 30 to 50 years of age. There are two approaches:

Screen And Treat Approach - single visit, community setting

HPV screen negative should be reassessed after 5-10 years while women living with HIV every 3-5 years.

HPV screen positive women who are suitable for ablative procedure should be treated and followed up after 12 months. VIA test with 3-5% acetic acid is recommended for deciding eligibility for ablative procedure. Those who are

screen positive but not eligible for ablative procedure should undergo LEEP. Cases with obvious growth or suspected cancer should be biopsied and managed accordingly.

VIA or Cytology Screen Negative cases should be re-screened after 3 years.

Cytology Screen Positive with ASCUS to be subjected to immediate triage with HPV DNA testing, if positive, do colposcopy, If HPV negative, rescreen after 3 years. Cases with abnormality above ASCUS or HPV positive should undergo colposcopy.

Screen Triage and Treat Approach - Multiple Visits, Hospital Settings

Triage may be done with partial genotyping, colposcopy, VIA or cytology as feasible.

HPV 16/18 or VIA Positive Triage should be taken up for ablative or excisional procedure as per eligibility. VIA triage negative cases with positive HPV DNA should undergo repeat HPV test after 2 years in general population and after one year in women living with HIV. Colposcopy and Cytology triage will be followed as per the respective reports.

Repeat HPV test should be done after 2 years for the general population or after 1 year for women living with HIV, after negative cytology screening test. On cytology

triage, cases with ASCUS should undergo colposcopy and biopsy, further management will depend on histology.

Cytology Positive Triage (where HPV test is not available for triage)

Women aged 25-29 years with ASCUS/LSIL should undergo repeat cytology annually twice. If repeats as ASCUS or above, colposcopy and biopsy should be done. If NILM, repeat cytology at 3yrs then routine age-specific screening.

Colposcopy and biopsy should be done in case of LSIL in women aged 30-64yrs.

ASC-H or HSIL should undergo colposcopy with biopsy and endocervical assessment.

ASC-H or HSIL in women desirous of pregnancy should undergo colposcopy and biopsy. If no CIN 2or3, repeat cytology and colposcopy 6 monthly for 2 yrs, if no high risk till 2 yrs, return to routine age specific follow up. If CIN 2/3 persist for 2 yrs on 6 monthly follow up, excisional procedure should be done.

In smears showing atypical endometrial cells or abnormal glandular cells, endometrial and endocervical curettage should be done first and along with colposcopy and biopsy.

Women with CIN may be completely asymptomatic and found to have CIN on routine screening or may present with vaginal itching, redness, dirty, foul smelling discharge or in advanced cases, may present with bleeding during intercourse or cervical examination. Colposcopy guided biopsy is the diagnostic test for CIN which gives histology of the lesion that can guide treatment.

A colposcope is a binocular stereoscopic microscope capable of at least 16× magnification, it has a centre light with green filter, and an adjustable stand. There are a variety of accessories, including adjustable magnification, real-time video, still cameras, ocular arms that allow simultaneous examination by a student or preceptor.

Colposcopy Procedure

Colposcopy is performed using a self retaining cusco's speculum, adjusted and fixed in vagina to visualise the whole of the cervix. Excess mucus and debris should be washed off the cervix with normal saline. Cervix is then inspected through the colposcope in a clockwise manner, concentrating on squamocolumnar junction. If no abnormality is seen on inspection, 5% acetic acid is applied on the cervix for one minute. Cervix is then inspected both with white light and green filtered light, which enhances vascular patterns. Abnormal colposcopic findings include acetowhite epithelium, punctation, leukoplakia, mosaicism, and atypical vessels.

Adequate Colposcopy - Entire transformation zone is

visualized clearly along with the entire extent of any lesion beginning at the transformation zone.

Inadequate Colposcopy - when complete visualization of transformation zone is not possible. In menopausal women, transformation zone migrates into the endocervix due to estrogen deficiency. An endocervical speculum may be useful or repeat colposcopy can be done after 4–6 weeks of vaginal estrogen therapy for better visualisation.

Transformation Zone is Classified as Per Findings of Colposcopy:

- Type 1TZ: The SCJ is located on the ectocervix and can be seen clearly.
- Type 2 TZ: The SCJ is located either fully or partially within the endocervical canal and can be seen with or without endocervical speculum.
- Type 3 TZ: The SCJ is located within the endocervical canal and is only partially visible or not at all visible, even with an endocervical speculum

Reporting of Colposcopy Findings- The International Federation of Cervical Pathology and Colposcopy (IFCPC - 2011) has provided a standard nomenclature for documentation of colposcopy findings. The reporting is based on Swede's score that has five parameters; lesion size, margins, vascularity, acetic acid and lugol's iodine uptake. Score of 0–4 correlates with normal/CIN1, 5–6 with CIN2/CIN3 and 7–10 correlates with CIN3/cervical cancer.

Colposcopic directed biopsy can be taken in swede score

above 5 with punch biopsy or Tischler's forceps. Diagnostic excisional procedure should be done in case of inadequate colposcopy. Endocervical curettage is indicated for Type 3 TZ, if no lesion is visible on the ectocervix, though the screening test is positive or when glandular abnormalities are suspected on cytology.

Management of Cervical Intraepithelial Neoplasia

CIN1 Management for Women Above 30 Years

If the preceding HPV test was positive or cytology showed ASCUS / LSIL, repeat screening at 1-2 yr, if negative should return to routine follow up. If CIN1 persists for 2 yrs, ablative or excisional procedures should be done. In case of preceding ASC-H or HSIL, diagnostic excision should be done. Ablative treatment may be used for non compliant cases.

CIN1 Management for Women Below 30 Years

If the preceding cytology was ASCUS / LSIL, repeat screen at 1 year. If the preceding cytology was ASC-H or HSIL, repeat screen at 6 months. If repeat test suggests ASC-H, HSIL or high grade lesion on colposcopy persisting for 1 yr, diagnostic excisional procedures should be done.

CIN2/3 Management in Women Not Desirous of Pregnancy

LEEP excision is treatment of choice for CIN 2, ablation should be done only if all criteria are met. Cold conization is recommended for CIN 3

CIN 2/3 Management in Women Desirous of Pregnancy.

For CIN3 with inadequate colposcopy, excisional procedure should be done.

For CIN2, if facility of ancillary test like p16 or Ki67 available, it should be done. Otherwise, colposcopy should be done at 6 months, if lesion persists one can directly go for excisional procedure, or can repeat cytology or colposcopy at 1 year. At any point, if high grade cytology is found or there is worsening of colposcopic findings, one should go for excisional procedures otherwise can repeat co-testing after 1 year.

CIN in Pregnancy - One must review colposcopy report, if colposcopy features of invasive cancer or inadequate colposcopy with CIN 3, counsel the patient and offer definitive treatment as per the period of gestation. If suggestive of invasive cancer with adequate colposcopy, defer treatment till after pregnancy.

The basic principles of treatment of CIN are as follows:

The whole transformation zone should be treated (excised or ablated), irrespective of the size of the lesion as the entire transformation zone undergoes HPV-induced clonal change and is at risk of developing CIN.

- CIN2 and CIN3 lesions should always be treated except in women younger than 25 years.
- The decision to treat a CIN lesion may be based on colposcopic findings (“see and treat”) without waiting for histological verification.

- VIA or HPV positive women can be treated by ablative or excisional procedures without colposcopic or histological verification ("screen and treat") in situations where there is unavailability of these diagnostic procedures.

Ablative Treatment Modalities- They involve tissue destruction that must extend up to 7–8 mm as the high-grade CIN lesions often extends into the crypts present in the transformation zone upto 5 mm.

Cryotherapy - The technique of cryotherapy depends on the destructive power of cold injury to the normal and neoplastic epithelial cells. Nitrous oxide (N2O) or carbon dioxide (CO2) gases are used to induce the freezing effect on the cervix. The temperature of either of the gases, when released to atmospheric pressure from a compressed state, drops to-60 to-80 °C. When the gas is applied to the cervix, the tissue temperature is reduced to-20 °C, causing permanent damage to the epithelial cells.The ectocervix has sparse sensory nerve endings. As a result, an ectocervical procedure like cryotherapy does not require any anaesthesia.

Eligibility for Cryotherapy - It should be used to treat only those CIN lesions that are limited to ectocervix without any extension to the endocervix or to the vagina. The transformation zone should be of type 1 and the lesion should not occupy more than 75% of the cervix. Cryotherapy probe should cover the lesion and there

should not be any suspicion of invasive cancer or glandular abnormality.

Thermal Coagulation

Thermal coagulation uses a probe called Semm coagulator which is heated to 100–110 °C for 20–45 seconds to boil the intracellular water and destroy both normal and abnormal cells of the transformation zone. Multiple applications of the probe are feasible with thermal coagulation. Hence, unlike cryotherapy, the technique is not limited by the disparity between the size of the lesion and that of the probe. The temperature used (100 °C) is lower than that used for electrocautery hence traditionally, this technique is known as "cold" coagulation.

The rest of the principles and indications for treatment by thermal coagulation are the same as those for cryotherapy. Thermal coagulation is as effective as cryotherapy in treating all CIN lesions with the advantage of use of electricity and more recently battery driven portable devices.

Excision Based Modalities

LEEP (Loop excision electrosurgical procedure) or LLETZ (Large Loop Excision of Transformation Zone).

This is indicated in cases that are not suitable for ablation. In addition there is advantage of obtaining tissue for histological evaluation. LEEP is also indicated for a CIN1 lesion that is persistent beyond 2 years, ASC-H or HSIL

with a type 3 transformation zone and no visible lesion on colposcopy, persistently abnormal cytology in the absence of any lesion visible on colposcopy LEEP may also be performed for Cervical glandular intraepithelial neoplasia (CGIN) (adenocarcinoma in situ) and Micro invasive cancer where cold-knife conization is preferred. Thus, it is a therapeutic procedure where lesion is on ectocervix otherwise it is essentially a diagnostic procedure to remove a "cone" for histopathological evaluation. During excisional treatment, the cone should be fashioned in such a way that the entire transformation zone, including the full length of the crypts, is removed.

Cold Knife Conization

This is an excisional method of treating high-grade CIN using a scalpel and removing a cone shaped portion of cervix in case of adenocarcinoma in situ, and microinvasive cancer. It can also be used in high-grade squamous lesions where upper limit is not visible, in settings where LLETZ facilities are not available.

The width and length of the cone will depend on the extent and the severity of the disease. The removed cone must include the entire transformation zone, the diseased epithelium, and adequate lesion free margin. The major advantages of CKC are that the specimen can be removed in a single piece and the margins are free of any thermal damage.

The procedure is more complicated than LLETZ and needs highly skilled providers, requires regional/general anaesthesia and hospitalization, and has higher

complication rates.

Persistent or residual disease is the persistence of a histopathological high-grade lesionat anytime interval after the initial treatment with no intervening documented absence of disease. Persistent or residual disease excludes cancers that have been confirmed after diagnosis with surgical specimen.

Recurrent disease is defined as detection of a histopathological high-grade lesion that was diagnosed from a biopsy or a subsequent surgical specimen (including hysterectomy, CKC and LLETZ) following a documented absence of high-grade lesions at any time interval after the initial treatment was performed.

FOLLOW-UP TESTS - Follow up is must if a woman is treated with ablation or LLETZ based on histopathology or without histopathology. It should be done at 12 months, if positive should be retreated with LLETZ followed by retesting within 12 months. Follow up recommendations are same for general population and HIV positive women.

Conclusion

Cervical Intraepithelial Neoplasia is the precursor of cervical cancer caused mostly by HPV infection. Screening for CIN through HPV testing, VIA or cytology and treatment of screen positive lesions with ablative and excisional procedures will definitely eliminate cervical cancer from the world. Spreading awareness of this knowledge and impacting these skills to all healthcare workers is the need of the hour.

Author: Prof. Rekha Sachan

Introduction

Human papillomavirus (HPV) causes significant morbidity and mortality in women and men.Human papillomavirus infection is associated with anogenital cancer (including cervical, vaginal, vulvar, penile, and anal) and oropharyngeal cancer (back of tongue, tonsil).HPV infection is sexually transmitted infection. More than 80% of sexually active females are infected with HPV infection in their lifetime. About 10% of women with HPV infection on their cervix will develop long-lasting HPV infections that put them at risk for cervical cancer. [CDC guidelines] Nearly all Cervical Cancer is due to HPV and two strains i.e.HPV16 and HPV18 account for 70% of cases. HPV infection causes 99 % of cervical cancer, 91 % of anal cancer, 75 % of vaginal cancer, 90 % of genital warts. Mortality and morbidity rate of HPV related cancers has decreased after introduction of HPV vaccine.

Vaccines For HPV Related Cancers

Three different vaccines, which vary in the type of HPV strain are-

- Human Papillomavirus Quadrivalent Vaccine (Gardasil) targets HPV types 6, 11, 16, and 18.
- Human Papillomavirus 9-valent Vaccine (Gardasil 9) targets the same HPV types as the quadrivalent vaccine (6, 11, 16, and 18) as well as types 31, 33, 45, 52, and 58.
- Human Papillomavirus Bivalent Vaccine (Cervarix) targets HPV types 16 and 18 was introduced but is not available now a days.

Whats New?

India has launched CERVAVAC vaccine (Serum Institute of India), on 24 January 2023.

It is a Quadrivalent vaccine (6,11,16,18) These are all prophylactic vaccines, designed to prevent initial HPV infection and subsequent HPV-associated lesions.

Timing and Doses For HPV Vaccine

· HPV vaccine is recommended for routine vaccination at age 11 or 12 years. Vaccination can be started at age 9 and should finish before 15 years.

· ACIP also recommends vaccination for everyone through age 26 years if not adequately vaccinated when younger. (HPV vaccination is given as a series of either two or three doses, depending on age at initial vaccination. WHO or IARC recommend that for girls below 15 years, single dose is also as effective).

· SAGE's review concluded that a single-dose Human Papillomavirus (HPV) vaccine delivers solid protection against HPV, the virus that causes cervical cancer, that is comparable to 2-dose schedules. The option for a single dose of the vaccine is cost effective, less resource intensive and easier to administer. It reduces the challenges of tracing girls for their second dose and allows for financial and human resources to be redirected to other health priorities.

· Vaccination is not recommended for everyone older than age 26 years. Some adults aged 27 through 45 years might decide to get the HPV vaccine based on discussion with their clinician, if they did not get adequately vaccinated when they were younger. HPV vaccination of people in this age range provides less benefit, for several

reasons, including that more people in this age range have already been exposed to HPV.

· For adults ages 27 through 45 years, clinicians can consider discussing HPV vaccination with people who are most likely to benefit. HPV vaccination does not need to be discussed with most adults over age 26 years.

In children with a history of sexual abuse or assault, the HPV vaccine should be given as early as possible, starting at age 9 years.

The HPV vaccine can and should be given to breastfeeding women age 26 years and younger who have not previously been vaccinated.

Route and Site of Administration- Intramuscularly in the deltoid region of the upper arm or in the higher anterolateral area of the thigh.

Contraindication for HPV Vaccine

1) A life-threatening allergic reaction to any ingredient of an HPV vaccine, or to a previous dose of HPV vaccine.
2) Those who are allergic to yeast (Gardasil and Gardasil 9).
3) Pregnant women

Side Effects of HPV Vaccine

The common side effects are pain, redness, or swelling in the arm where the shot was given, fever, headache or feeling tired, nausea, muscle or joint pain.

Author: Prof. Nisha Singh

Cervical Cancer in India is a Preventable Tragedy that Requires Urgent Attention.

Cervical cancer accounts for 9.4% of all cancers and 18.3% of new cases. Cervical cancer ranks second amongst cancers in Indian women and it is the most common genital cancer in India. It has a bimodal distribution with one peak at 35 to 39 years and another peak at 60 to 64 years.

Symptoms of Cervical Cancer

- Postmenopausal bleeding
- Postcoital Bleeding
- Pain lower abdomen
- Blood stained and Offensive discharge

Signs of Cervical Cancer

Speculum Examination

- An exophytic cauliflower like growth is seen in 80% cases
- Ulcerative growth is seen in 20% cases
- The growth bleeds on touch
- Cervical os may or may not be visualized

Growth may be extending to adjacent vaginal walls

Exophytic Growth

Ulcerative Growth

Bimanual Vaginal Examination

- Confirm cervical findings- size, shape, and extent of growth
- Uterus is usually normal in size, may be enlarged in pyometra.
- Parametrial involvement (is felt through lateral and posterior fornices of the vagina)

Rectal Examination

- Cervical size and Consistency .
- Parametrial extension of disease
- Induration of uterosacral ligaments can be appreciated.
- Rectal mucosa may be free or involved.

In, some advanced cases cervical /inguinal lymph nodes may be palpable.

Histopathology

The most common histological type is squamous cell carcinoma. Endocervical adenocarcinoma may be seen in about 20% cases. Majority of both squamous cell carcinoma and adenocarcinoma are HPV- associated.

Diagnosis

- Cervical biopsy is mandatory for confirming the diagnosis. A punch biopsy from junction of normal and abnormal tissue is taken and sent for histological evaluation.
- MRI abdomen and pelvis is used for pre-op staging (extent of disease)

- CT scan is useful for nodal metastasis
- Chest X-ray helps to exclude pulmonary metastasis.

Staging of Cervical Cancer - As per FIGO 2018, imaging and pathology can be used ,where available ,to supplement clinical findings with respect to tumor size and extent in all stages. For all surgically treated cases, final staging is as per histological findings.

Figo 2018 Ca Cervix Staging

Stage	Description
I	Carcinoma is strictly confined to the cervix (extension to the uterine corpus should be disregarded)
IA	Invasive carcinoma that can be diagnosed only with microscopy, with maximum depth of invasion <5 mm
IA1	Stromal invasion <3 mm in depth
IA2	Stromal invasion ≥3 mm and <5 mm in depth
IB	Invasive carcinoma confined to the uterine cervix, with measured deepest invasion ≥5 mm
IB1*	Tumor measures <2 cm in greatest dimension
IB2*	Tumor measures ≥2 cm and <4 cm in greatest dimension
IB3*	Tumor measures ≥4 cm in greatest dimension
II	Carcinoma invades beyond the uterus, but has not extended onto the lower third of the vagina or to the pelvic wall
IIA	Limited to the upper two-thirds of the vagina without parametrial involvement
IIA1	Tumor measures <4 cm in greatest dimension
IIA2	Tumor measures ≥4 cm in greatest dimension
IIB	With parametrial involvement but not up to the pelvic wall
III	Carcinoma involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or nonfunctioning kidney and/or involves pelvic and/or para-aortic lymph nodes
IIIA	Involves the lower third of the vagina, with no extension to the pelvic wall
IIIB	Extension to the pelvic wall and/or hydronephrosis or nonfunctioning kidney from tumor
IIIC*	Involvement of pelvic and/or para-aortic lymph nodes, irrespective of tumor size and extent†
IIIC1*	Pelvic lymph node metastasis only
IIIC2*	Para-aortic lymph node metastasis
IV	Carcinoma has extended beyond the true pelvis or has involved (biopsy-proven) the mucosa of the bladder or rectum
IVA	Spread to adjacent pelvic organs
IVB	Spread to distant organs

Author: Prof. Nisha Singh

The treatment of cervical cancer is based on stage of disease that may be assessed by clinical findings and appropriate imaging techniques.

Surgery is the mainstay of treatment for early disease and for fertility preservation. The various surgical techniques available for treatment of different stage of disease need surgical training and expertise available with gynaecologic onco surgeons. Hence these cases should be handled by experts only.

Radical Hysterectomy classification previously given by Piver and Rutledge (Type 1-5) has now been widely replaced by that given by Querlow and Murrow (Class A-D).

Principles of Surgical Treatment

The aim should to be select a case that has minimal chances of lymph node metastases because patient should ideally be treated with single treatment modality. Preoperative MRI is the best suited modality for the same.

In addition the dissection should be adequate choosing correct surgical procedure so that surgical margins are free of disease.

Adequate care should be taken while doing lymphadenectomy and handling ureter, bladder or bowel to reduce postoperative morbidity.

Stage wise treatment protocol is shown in the table below;

STAGE	FERTILITY NOT DESIRED	FERTILITY DESIRED
1A1	Extra fascial Hysterectomy or Simple Hysterectomy	Theraputic Conization
1A2, 1A1 with LVSI Stage1B1, Stage IIA1 (maximum diameter < 2cm)	Modified Radical hysterectomy with bilateral pelvic lymphadenectomy	Radical trachelectomy with bilateral pelvic lymphadenectomy
IB2 IIA1(maximum diameter >2 but <4 cm)	Type III (Class C) Radical Hysterectomy with pelvic lymphnode dissection Followed by adjuvant chemotherapy if needed	
IB3 IIA2 and above	Radiotherapy with concurrent chemotherapy	

Adjuvant Therapy

Post surgical Adjuvant chemoradiation is required in cases of

1. Positive surgical margins
2. Lymph node metastasis
3. Tumor>4 cm
4. LVSI positive
5. Deep stromal invasion >1/3

Chemoradiation

Concurrent chemoradiation is well suited for advanced disease or poor surgical candidates with early disease. Use of image modulated radiation and addition of

chemotherapy has greatly increased the efficacy and reduced the morbidity associated with radiation treatment.

External beam Radiation (EBRT) is usually given in 25 fractions spread over 5 weeks with weekly cisplatin therapy. This is followed by 3 courses of intracavitary radiation (ICRT).

Conclusion

Overall prognosis of cervical cancer is good in cases treated both by surgery or chemoradiation. Only the stage 4 disease with bladder bowel involvement or distant metastasis has poor prognosis.

Section

2

Vulvar Cancers

1. Clinical Features and Diagnosis of Vulvar Cancer
2. Treatment Overview of Vulvar Cancer

Fig 1 : Early - Stage Vulvar Cancer

Author: Dr. Shalini Singh

Introduction

Vulval cancer is a rare cancer predominantly affecting elderly women and is uncommon below the age of 50 years. No screening test has shown benefit in screening the unselected population for vulvar cancer. Lichen sclerosis and infection with high-risk HPV types are predisposing factors for squamous neoplastic changes. Typically, HPV-related disease is seen in younger women and may be multifocal. With increasing HPV infection, the incidence in women aged 40–49 years has risen two-fold.

Clinical Features

The clinical presentation varies according to the stage of disease. Women often have difficulty articulating vulval symptoms to medical practitioners and all women with vulval symptoms should be examined. Vulval cancers are sometimes diagnosed on examination during another procedure, for example, colposcopy or catheterization. Often these are not asymptomatic, but the women have either not presented for diagnosis, or not been appropriately referred. Many a time, diagnosed during follow-up for pre-existing vulval disease e.g., lichen sclerosis or VIN.

While the need to take a full history is self-evident, specific questioning will also be required. Women often self-medicate with over-the-counter topical preparations that can exacerbate the symptoms of vulval cancer. Advice regarding the care of the vulva and omitting these medications form an important part of management.

Symptoms of vulval cancer include vulval itching, irritation, or pain. Women may also notice a lump, bleeding, or discharge. If an unexplained vulval lump or an ulcer is found, an urgent specialist referral should be made. For a patient who presents with pruritus or pain and where cancer is not immediately suspected, it is reasonable to use a period of 'treat, watch, and wait' as a method of management. But this should include active follow-up until symptoms resolve or a diagnosis is confirmed. Any colour change (whitening or pigment deposition), elevation or irregularity of the surface, contour, lump, ulcer, or warts in a postmenopausal woman should be biopsied.

Examination Findings strongly indicating vulval cancer include an irregular, fungating growth, an irregular ulcer or a lump, and enlarged groin nodes. Any involvement of the vagina, urethra, base of the bladder, or anus should be noted. Large tumors should be palpated to assess whether it is infiltrating deep to the pubic and ischial bones.

The examination may have to be performed under local anaesthesia because of the pain often associated with large tumours. The presence or absence of groin lymphadenopathy should also be noted.

Diagnosis

The cornerstone of diagnosis is a punch biopsy from the margin of the lesion including both abnormal and normal area. Lesions should be biopsied rather than excised thus avoiding removal of the whole lesion. Diagnostic biopsies should be of a sufficient size (greater than 1 mm depth to allow differentiation between superficially invasive and

frankly invasive tumors) and orientated to allow quality pathological interpretation. This can be done under local anesthesia with a 3 or 4 mm Keyes biopsy instrument, or with an incisional or wedge biopsy. Even if the lesion is small, it is better not to excise the entire lesion at the time of biopsy, as this makes the subsequent surgery difficult to be planned.

Histopathological Types

Squamous cell carcinomas (SCCs) account for most vulvar cancers (more than 80%), and melanomas are the next most common cancer. Rarer histological types include:

- Basal cell carcinoma
- Verrucous carcinoma
- Adenocarcinoma related to extra-mammary Paget's disease
- Bartholin gland carcinoma (squamous, adeno carcinoma, or transitional cell carcinoma)
- Sarcoma

Histological grades can be, well-differentiated (G1), moderately differentiated (G2), poorly or undifferentiated (G3) GX : Grade cannot be assessed.

Once the cancer is confirmed, the patient should be referred to a gynaecological cancer centre to be reviewed by the multidisciplinary team prior to radical treatment.

Author: Dr. Shalini Singh

Introduction

Ninety percent of all vulval cancers are squamous cell carcinomas, with melanoma, Paget's disease, Bartholin gland tumours, adenocarcinoma, and basal cell carcinoma accounting for most of the remaining tumours. The histology is important, as it represents a variable in determining the likelihood of lymph node involvement. Lymphovascular space invasion (LVSI) and infiltrative growth patterns are markers of poor prognosis.

Vulval cancer spreads either by direct extension to adjacent structures or through lymphatics to the inguinal and femoral nodes (the regional lymph nodes) or by haematogenous spread. Overall, about 30% of women with operable disease have nodal spread. The 5-year survival in cases with no lymph node involvement is in excess of 80%. This falls to less than 50% if the inguinal nodes are involved and 10–15% if the iliac or other pelvic nodes are involved.

Principles of Treatment

The treatment of vulval cancer is primarily by surgery. This has become more individualised and conservative over the years. Yet, the need for adequate resection margins (1 cm after tissue fixation) and groin node dissection or evaluation remains important basic principles. Management may vary considerably from quite simple to very complex surgery. Each case should be considered on its merits and an agreed plan of management devised by the gynaecological cancer team.

Factors such as tumour size, location, medical fitness and the wishes of the patient will all influence management.

Treatment of Microinvasive Vulvar Cancer (Stage IA)

Stage IA vulvar carcinoma is defined as a lesion measuring 2 cm or less in diameter, with a depth of invasion of 1.0 mm or less. Depth of invasion is measured from the basement membrane of the deepest, adjacent, dysplastic, tumor-free rete ridge to the deepest point of invasion. These lesions should be managed with radical wide local excision, and groin node dissection is not necessary.

Treatment of Early Vulvar Cancer

Early vulvar cancers are those confined to the vulva, and where there are no suspicious lymph nodes, either on clinical examination, ultrasound, or cross-sectional radiological assessment. This includes stage IB and stage II disease.

The gold standard of treatment for early vulvar cancers is radical wide local excision of the tumor. Associated preinvasive disease should also be excised to exclude any other areas of invasion, and to prevent new tumors arising in the so-called “abnormal field.” While the surgeon should aim for surgical margins of 2 cm to achieve pathological margins of at least 8 mm (allowing for shrinkage of the fixed tissue), it is now recognized that many “recurrent” vulvar cancers are probably new tumors that have developed in the surrounding abnormal tissue, rather than recurrences due to inadequate margins.

With most tumors, primary closure is possible, but consideration should be given to reconstructive surgery for closure of large defects, and for maintenance of vaginal function. When reconstruction is necessary, three of the most commonly utilized flaps include the V–Y flap, rhomboid flap, and gluteus maximus myocutaneous flap.

Inguinofemoral Lymphadenectomy

The appropriate management of the groin lymph nodes is the most important factor in reducing mortality from early vulvar cancer, as recurrences in the groin are associated with poorer survival despite using multimodal therapies as "rescue" treatments. The current standard involves resection of the primary tumor and lymph nodes through separate incisions. This approach allows better healing compared with en bloc resection of the vulva and groins. Both inguinal and femoral nodes should be removed, as inguinal node dissection alone is associated with a higher incidence of groin recurrence.

All women who have Stage IB or resectable Stage II cancers should have an inguinofemoral lymphadenectomy. Less than 1% of patients who have small lateral lesions (less than 4 cm and ≥2 cm from the vulvar midline) and negative ipsilateral nodes have metastases in the contralateral groin nodes, and therefore an ipsilateral groin dissection is adequate treatment for these patients.

Patients who have tumors closer to (<2 cm) or crossing the midline, especially those involving the anterior labia minora, and those women who have very large lateral

tumors (>4 cm), or positive ipsilateral nodes, should have a bilateral groin node dissection.

Sentinel Node Biopsy: The aim of the procedure is to detect nodal metastases in the "sentinel" node (which primarily drains the tumor), and then to omit a full lymphadenectomy in sentinel node negative patients, thereby decreasing the morbidity associated with a complete inguinofemoral node dissection.

Indications for a sentinel node procedure are:

1) Unifocal tumors confined to the vulva
2) Tumors less than 4 cm in diameter
3) Stromal invasion more than 1 mm
4) Clinically and radiologically negative groin nodes

Sentinel lymph nodes are identified using both radio-labelled technetium and blue dye. Recently, Indocyanine green dye used with near infrared florescent technology has become an option for sentinel node detection.

Of note, when an ipsilateral sentinel lymph node is not detected, a complete ipsilateral inguino femoral lymphadenectomy must be done. In addition, if an ipsilateral sentinel lymph node is positive, a complete bilateral inguino femoral lymphadenectomy is recommended.

Adjuvant therapy in Early Stage Cancer

Indications for pelvic and groin irradiation in patients with positive groin nodes are:

- Presence of extra capsular nodal spread.

- Presence of metastases in two or more groin nodes.

In terms of radiotherapy, radiation fields during external beam radiotherapy (EBRT) should include the inguino femoral and external and internal iliac lymph nodes in most patients. If there are many or bulky positive inguinal nodes, or if pelvic node metastases are suspected, the upper border of the radiation field might be extended.

Management of Advanced Vulvar Cancer

Advanced vulvar cancer includes tumors that extend beyond the vulva and lower third of vagina, and/or where there are bulky positive groin nodes. The management of women with advanced vulvar cancer is complex and should be individualised and carried out by a multidisciplinary team.

When confronted with advanced vulvar cancer, the status of the groin nodes should be determined before treatment is planned. Patients with clinically suspicious nodes should have fine needle aspiration or biopsy of the nodes. Pelvic CT, MRI, or PET-CT may be helpful in determining the extent of inguino femoral or distant metastatic disease.

If there are no suspicious nodes either clinically or on imaging, bilateral inguino femoral lymphadenectomy may be performed; if the nodes are negative, radiotherapy to the groins and pelvic nodes will not be necessary. However, if histology reveals positive nodes, then adjuvant radiotherapy or chemo radiation to the groin and pelvis should be offered as for early-stage disease.

In patients who have clinically positive nodes, enlarged groin and pelvic nodes should be removed if possible, and

the patient given postoperative groin and pelvic radiation. Full lymphadenectomy should not be performed because a full groin dissection followed by groin irradiation may result in severe lymphedema.

In terms of the management of the primary tumor, surgical excision of the primary tumor with clear surgical margins and without sphincter damage, whenever possible, constitutes the optimum way to treat advanced vulvar cancer, as well as to palliate symptoms such as local pain and offensive discharge.

Primary Chemo-Radiation

In cases where surgery is thought to be inappropriate for the individual patient, primary chemoradiation may be used to treat the primary tumor as well as the groin and pelvic nodes.

Ulcerated or fixed groin lymph nodes should be biopsied to confirm the diagnosis, and then treated with primary radiotherapy, with or without chemosensitization. If there is an incomplete response to radiation, the nodes may then be resected if appropriate.

An alternative strategy is the use of neoadjuvant chemotherapy with cisplatin or carboplatin and paclitaxel, to shrink the nodes prior to radiotherapy. If adequate excision of the primary tumor can only be achieved by exenteration and the formation of a bowel or urinary stoma, radiotherapy (with or without concurrent chemotherapy) may be a preferred treatment alternative.

Survival is improved if any post-radiation residual tumor is resected.

Concurrent chemo radiation is a well-described treatment alternative for those patients with large tumors in whom primary surgical resection would damage central structures (anus, urethra), and long-term complete responses have been reported. The groin nodes and pelvis may need to be included in the radiation field depending on the status of the groin nodes, as determined initially.

Recurrent Disease

The management of recurrent disease is often difficult, and treatment options depend on the site(s) of the recurrence, the performance status of the patient, and what previous treatment has been given, as well as the findings of re-staging investigations. Options for treatment include surgery, (chemo)radiation, neoadjuvant or palliative chemotherapy, a targeted agent (if available), or best supportive care.

Follow-up

Local recurrences most often occur in the first 2 years after treatment, and most women with gynaecological malignancies are seen every 3–6 months for the first 2 years, and then every 6–12 months until at least 5 years. The surveillance visit should include a review of symptoms relevant to recurrence or adverse effects of treatment, and thorough clinical examination.

Conclusion

Vulvar cancer treatment is predominantly surgical, particularly for SCC, although concurrent chemoradiation is an effective alternative for advanced tumors or

inoperable cases. Management should be individualized, and carried out by a multidisciplinary team in a dedicated gynecologic cancer centre.

Section

3

Hereditary Gynecological Cancers

1. Hereditary Gynecological Cancers

Author: Prof. Nisha Singh

Introduction

Hereditary cancer is one that has genetic predisposition and transfer of mutated genes in the offsprings can put them at high risk of such cancers

Hereditary cancer syndromes [HCS] are defined as syndromes, where the genetics of cancer are the result of low penetrant polymorphisms or of a single gene disorder inherited in a mendelian fashion .During the last decade, compelling evidence has accumulated that approximately 10-15% of all cancers can be attributed to hereditary cancer syndromes.

Some of the identified hereditary gynaecological cancer syndromes are –

- Hereditary breast and ovarian cancer (HBOC)- [BRCA1, BRCA2];

-Lynch syndrome (endometrial and ovarian cancer) [MLH1, MSH2, MSH6, PMS2, EPCAM);

- Li-Fraumeni syndrome [TP53] associated with ovarian cancer;

- Cowden syndrome [PTEN] associated with endometrial cancer;

-Peutz-Jeghers syndrome [STK11] associated with ovarian and cervical cancer. Other gene polymorphisms include RAD51C, RAD51D associated with ovarian cancer and DICER1 with Sertoli-Leydig cell tumor (SLCT) of the ovary.

Of all gynaecological cancers, ovarian cancer is most often associated with an inherited susceptibility gene, which can occur in about 20% of cases.

The risk of cancer inheritance is indicated in women with the following features:

- Presence of different types of cancers in same woman
- Multiple primary tumors in the same organ (such as the breast or colon), in a single individual
- Several close blood relatives having the same type of cancer, especially when blood relatives are on the same side of the family
- Unusual presentation of a specific type of cancer (*e.g.*, breast cancer in a man)
- The presence of specific benign conditions, specifically skin growths or skeletal abnormalities, that are known to be associated with inherited cancer syndromes
- Women with the below features are at high risk of hereditary breast cancer:
  - Age at onset <50 years
  - Triple-negative breast cancer (lack of expression of estrogen and progesterone receptors and lack of ERBB2 (also known as HER2 or HER2/neu) overexpression, (suggesting hereditary breast and ovarian cancer syndrome [30% when less than age 60 years].
- Probability of occurrence of ovarian/endometrial cancer is high in women with below features:

- Epithelial ovarian cancer, fallopian tube cancer, or peritoneal cancer, especially serous histology (suggesting hereditary breast and ovarian cancer syndrome [10–15%])
- Colorectal cancer with DNA mismatch repair deficiency (suggesting Lynch syndrome [24%])
- Endometrial cancer with DNA mismatch repair deficiency (suggesting Lynch syndrome [12%])" .

Genetic testing is performed using a panel of multiple genes through next generation sequencing technology. This multigene testing process increases the likelihood of finding variants of unknown significance and it also allows for testing for pathogenic and likely pathogenic variants in multiple genes that may be associated with a specific cancer syndrome or family cancer phenotype.

Section

4

Endometrial Cancer

1. Clinical Features and Diagnostic Methods
2. Treatment overview of Endometrial Cancer

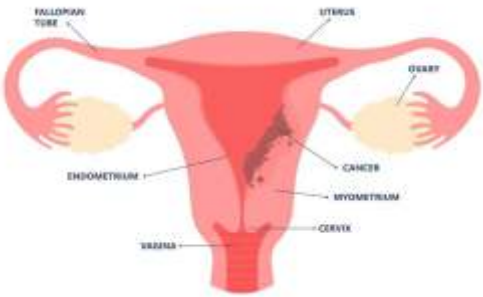

Fig 2- CA Endometrium - Primary Site of Tumor

Author: Prof. S.P. Jaismar

Introduction

Endometrial cancer is the sixth most common cancer, with 417 000 new cases and 97 000 deaths in 2020. It is the most frequently diagnosed cancer in females with the greatest incidence in high-income countries. The incidence of endometrial cancer is rising alongside the growing obesity. In developing countries including India, endometrial cancer is seen in 1.8 per 100,000 population. The peak incidence of endometrial cancer is at 55-70 years, 20-25 % occur in peri menopausal women and only 5% develop in women below the age of 45 years when they are well differentiated and have good survival. Most women with endometrial cancer are diagnosed at an early stage and have highly curable disease, reflected in excellent 5-year survival rates. Patients presenting with adverse clinico pathological characteristics have biologically aggressive endometrial cancer phenotypes with poor prognosis.

Risk Factors

Most of the risk factors are related to prolonged, unopposed estrogen stimulation of endometrium like nulliparity, late menopause, Tamoxifen therapy and atypical endometrial hyperplasia. Obesity, hypertension, diabetes mellitus and LYNCH II syndrome (hereditary non polyposis colorectal cancer syndrome) are other risk factors. Endometrial cancer may be asymptomatic in 7-10% cases.

Signs and Symptoms

About 90% of women with endometrial carcinoma have abnormal premenopausal or postmenopausal vaginal bleeding, pain or discharge as their only presenting symptoms. The clinical signs of endometrial cancer include a normal or enlarged uterus on bimanual examination. In advanced cases, the cervix, parametrium or adnexa may be involved. Serous variety presents with ascites and peritoneal metastasis similar to ovarian cancer.

Histopathological Classification

Endometroid Adenocarcinoma(80%)

Mucinous Carcinoma(5%)

Papillary Carcinoma

Clearcell Carcinoma(<5%)

Squamous Carcinoma(rare)

Undifferentiated Carcinoma

Mixed Carcinoma

Clinico PathologicalTypes of Endometrial Cancer

	TYPE 1	TYPE 2
Risk factors	Unopposed estrogen	Age
Age	Perimenopause	Postmenopause
Endometrial hyperplasia	present	Absent
Tissue differentiation	well	Poor
Myometrial invasion	minimal	Deep
Histology	Endometrioid	Serous,clear

Molecular Characters of endometrial cancer

Molecular characters	TYPE 1	TYPE 2
Ploidy	Polyploid	Aneuploid
HER2/neu overexpression	No	Yes
P-53	No	Yes
PTEN mutation	Yes	No
Prognosis	Favorable	Not favorable

FIGO STAGING	CHARACTERISTICS
Stage I	Tumor confined to corpus
StageIA	uteriNo or less than half
Stage IB	invasion
	Invasion equal to or more than half of the myometrium
Stage II	Tumor invade cervical stroma, but does not extend beyond uterus
Stage III	Local and /or regional spread of tumor
Stage III A	Tumor invades the serosa of corpus uteri and /or
Stage III B	adnexaeVaginal and /or parametrial involvement
Stage III C	Metastasis to pelvic and /or paraaortic lymph
III C 1	nodesPositive pelvic lymph node
III C 2	Positive para-aortic lymph nodes with or without positive pelvic lymph nodes
Stage IV	Tumor invades bladder and/or bowel mucosa, and/or distant
Stage IV A	metastasisTumor invades bladder and/ or bowel mucosa
Stage IV B	Distant metastasis including intra-abdominal and/or inguinal lymph node metastasis

FIGO Grading

GRADE1-<5% non-squamousor non-morular growth pattern

GRADE2- 6-50% non-squamous or non-morular growth pattern

GRADE 3->50%non-squamousor non-morular growth pattern

Poor Prognostic Variables - Increasing Age, non endo metriod histology, Grade 2 or 3, tumor size > 2cm, increasing depth of myometrial invasion, lymph vascular space invasion, isthmus and cervical extension, positive peritoneal cytology, aneuploid and high proliferative index of tumor.

ER PR Receptor Positive Cases have good prognosis.

Screening for Endometrial Cancer

Screening is not recommended in general population.

For high risk group (eg : Lynchsyndrome) screening can be done with TVS & aspiration biopsy. Its should be started at 35yrs, continued annually until hysterectomy.

DIAGNOSIS

Transvaginal Sonography - Endometrial Thickness is assessed as per menopausal status. A cutoff value of 4 mm is taken for menopausal women and 16 mm for premenopausal women. Any intracavitary growth irregular endometrium is also considered suspicious.

Endometrial Biopsy - Office Endometrial Aspiration Biopsy is the first step in diagnosing endometrial

carcinoma with 90-98%accuracy. Hysteroscopy Guided Biopsy should be done in patients with focal endometrial growth or thickening, irregular endometrium, cervical stenosis, recurrent bleeding after negative endometrial biopsy or if specimen obtained is inadequate on EA.

Liquid Based Cytology (LBC) and Endocervical Curettage (ECC) may be performed to rule out coexisting cervical pathology.

MRI Abdomen and Pelvis is useful for detecting invasion into the myometrium and lymph node metastasis.

Chest Xray is added for lung metastasis.

Surgery is the Mainstay of treatment for endometrial cancer and is decided as per the preoperative assessment of stage of disease based on clinical examination and imaging.

1) Stage IA GI or II, Endometroid histology - Extrafascial Total Abdominal Hysterectomy with Bilateral Salpingo Oophorectomy (TAH with BSO).

2) Stage IB or IA GIII or Non-Endometroid Histology or Tumor >2 cm or Stage II - TAH with BSO with pelvic and para-aortic lymphadenectomy

3) **Serous Histology-** TAH BSO with omentectomy and peritoneal biopsy

4) **Stage III -** Debulking surgery- TAH with BSO with omentectomy, removal of abdominopelvic metastasis and enlarged nodes

5) **Stage IV**- Neoadjuvant chemotherapy f/b cytoreductive Sx.

Vaginal bleeding/pain from local tumor/leg edema: pelvic radiotherapy

Choice of Surgical Approach

RCTs show superiority of minimally invasive approaches. Considerations during MIS hysterectomy include use of uterine manipulator to facilitate exposure and avoidance of power morcellator to remove uterus .

MIS may be difficult in cases with excessive uterine size, contraindication to trendelenburg position.

Sentinel lymph node biopsy can safely replace complete lymadenectomy where needed.

Adjuvant Therapy :

Low risk Stage IA, grade 1-2, endometroid, LVSI negative	Staging laparotomy+ extrafascial hysterectomy+ BSO± omentectomy± sampling of pelvic and para-aortic lymph nodes No adjuvant therapy
Intermediate risk Stage IB, grade 1-2, endometroid, LVSI negative	Surgery as above+ Adjuvant brachytherapy
High Intermediate risk Stage IA, grade 3, endometroid (regardless of LVSI); Stage IA/IB, Grade 1-2 endometroid with LVSI positive	Nodes negative on nodal biopsy: Adjuvant brachytherapy Nodal staging not done but HPE shows grade 3 tumor with no LVSI: Adjuvant brachytherapy Nodal staging not done but HPE shows grade 3 tumor with LVSI: Adjuvant external beam radiation therapy (EBRT)
High risk Stage IB grade3, II, III endometroid with no residual disease, non-endometroid histology	Stage I: Adjuvant EBRT± adjuvant chemotherapy if nodal staging not done Stage II: Grade 1-2, LVSI negative: Vaginal brachytherapy Grade3/LVSI positive/nodal staging not done: Adjuvant EBRT± Vaginal boost± adjuvant chemotherapy Stage IIIA,IIIB,IIIC1: Chemotherapy + EBRT IIIC2: Chemotherapy + extended field EBRT
Advanced Stage III residual disease, IVA	Systemic therapy (chemotherapy or hormonal)
Metastatic IVB	Systemic therapy (chemotherapy or hormonal)

Special Considerations

Diagnosis Post Hysterectomy: If grade3 lesion, deep myometrial invasion, or LVSI – remove adnexa or adjuvant EBRT

Medically in Operable Patient : Most common reason is morbid obesity or severe cardiopulmonary dysfunction. Primary radio therapy is an option Well differentiated lesion, contraindication to general anesthesia, unsuitable for radio therapy can be treated with high dose progestins

or intrauterine hormone releasing device.

Diagnosis in Young Women: Uncommon, can be confused with severe atypical hyperplasia. Fertility preservation only recommended in grde1 tumor with nomyometrial invasion. Progestins (megestrol acetate 160-320mg/d or MPA400-600mg/d) may be given with LNG-IUS should be continued as long as disease is static or inremission. Hysterectomy is recommended once child bearing is complete

Targeted Therapy: Includes drugs targeting molecular pathways vital to cancer survival. The drugs available are Temsirolimus, deforolimus, & everolimus (mTOR inhibitors), Bevacizumab (angiogenesis inhibitor) as single agent or withpaclitaxel & carboplatin, Geftinib (tyrosine kinase inhbitor), Palbciclib (CDK4/6 inhibitor) and Trastuzumab (Her2/neu receptor)

Follow- Up:

- ACOG recommends follow-up every 3-4 months for 2-3 yrs, then every 6 month, annually after 5yrs
- Routine chest X-ray & vaginal cytology not recommended
- Pelvic examination & symptoms directed examination is recommended
- High risk for other cancer so life style modification advocated

Recurrence:

- Main stay of treatment is surgery, radiation therapy or both
- Non localised tumors are treated with progestin therapy : MPA 50 - 100 mg TDS or megesterolacetate 80mg BD or TDS
- Platinum based chemotherapy (cisplatin & doxorubicin or carboplatin & paclitaxel) is recommended for patient with advanced or recurrent disease not amenable to cure by surgery and/or radiotherapy.

Section

5

Ovarian Cancer

1.Clinical Features of Ovarian Cancer

2.Diagnostic Modalities in Ovarian Cancer

3.Treatment Overview of Ovarian Cancer

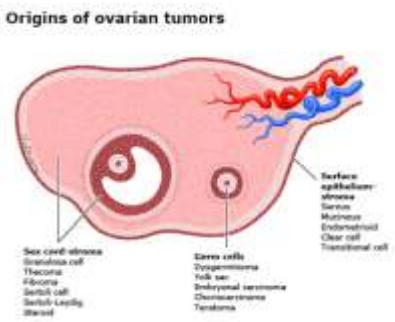

Fig 3-

CA Ovary - origin of different types of ovarian cancer

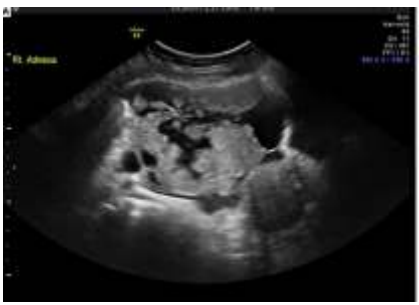

Fig 4-

USG picture of a malignant ovarian mass

Author: Prof. Renu Singh

Introduction

Ovarian cancer is the commonest cause of death from gynaecological cancers though it is the second most common gynecologic cancer in the world. The reason being that majority of the patients are diagnosed at an advanced stage. Early stage disease is potentially curable. Unfortunately, robust screening programs for ovarian cancer using pelvic imaging or tumor markers have not yet been successful. Early identification of ovarian neoplasm at present relies on symptom recognition in at risk individuals.

Symptoms related to the disease occur in many patients even at early stage of the disease. The early detection of ovarian cancer through symptom recognition relies on the following clinical approach.

History Taking

The symptoms of ovarian cancer in the early stages may be minor, transient and may be ignored by the patient and the physician. While elucidating history, it is important to focus attention on women who are at increased risk, like women over 40 years or with a family history of ovarian or related cancers. Women with infertility, having endometriosis (clear cell, endometriod carcinoma) are at increased risk of ovarian neoplasms.

The menstrual history should be enquired in detail. A change in the pattern of menstrual bleeding in premenopausal women or appearance of postmenopausal bleeding is alarming. The contraceptive history should include past use of oral contraceptives as its

use over 5 years has a protective effect. The history should also include the duration of breastfeeding if any. As past breastfeeding for > 12 months has a protective effect. History of cigarette smoking puts the woman at increased risk of mucinous carcinoma.

It is probably most effective to focus attention to symptoms like abdominal bloating, urinary urgency or frequency, difficulty eating or feeling full, having abdominal or pelvic pain in these women. One may attribute these nonspecific symptoms because of gastrointestinal problems. Patients who complain about these symptoms should be evaluated further with a thorough history. The frequency and severity of these symptoms must be enquired. Abdominal pain and or discomfort, abdominal swelling or bloating are more common, recur more frequently and are more severe in these patients prior to the diagnosis of ovarian cancer. The pattern and quality of symptoms are also important. Symptoms in these women occur more frequently (20 to 30 times versus 2 to 3 times per month), are more severe and have a shorter duration (less than 3 to 6 months versus one year or more). Further, in premenopausal women changes in the menstrual cycle pattern is an important symptom. Symptoms of intestinal obstruction, ascites /pleural effusion causing cough or breathlessness may be the presenting complaint.

Frequency of symptom categories in women with ovarian cancer

Type of symptom	Percent
Abdominal	77
Gastrointestinal	70
Pain	58
Constitutional	50
Urinary	34
Pelvic	26

Symptom Index:

A symptom index has been developed to aid in evaluating patients with early ovarian cancer but is not yet recommended for routine clinical use. The symptom index is considered positive if a patient report any of the following symptoms that are:

- New to the patient within the past year
- Occur more than 12 times per month

1) Pelvic or abdominal pain
2) Increased abdominal size or abdominal bloating
3) Difficulty eating or feeling full quickly

Physical Examination:

Woman suspected of having symptoms of ovarian neoplasm should undergo thorough general, abdominal, pelvic and rectovaginal examination. Breast examination as well as palpation of lymph nodes in the cervical (especially supraclavicular), inguinal and axillary regions are an important component in the general examination. Following findings on examination are suggestive of ovarian neoplasm:

- Adnexal mass
- Abdominal ascites
- A mass in the mid to left upper abdomen, which may represent an omental cake
- Pleural effusion
- Groin or supraclavicular lymphadenopathy
- Nodules in Pouch of Douglas on vaginal or rectal examination

In cases with normal findings on physical examination, depending upon the clinical situation, one may wait for 2-4 weeks to observe if the symptoms resolve or not. However, it is better to obtain an ultrasound examination of the abdomen and pelvis to supplement the decision-making process.

Author: Prof. Renu Singh

Introduction

Wherever there is a suspicion of ovarian cancer on clinical examination, the following investigations should be advised.

1. Imaging Studies: Ultrasonography of the abdomen and pelvis (transvaginal and transabdominal) is usually the first investigation for diagnosing an adnexal mass and or ascites or of symptom complex suggestive of ovarian mass. Presence of a complex mass with internal septae, solid areas, internal echoes or papillary projections may indicate malignancy. Color doppler may show vascularity in the internal sepatae. CT scan of chest, abdomen and pelvis are recommended to fined extraovarian speed and CT scan of chest is the recommended modality of choice for extraovarian spread. Imaging findings of ascites, thickened omental areas, presence of lymph nodes metastasis help in diagnosing the nature of ovarian neoplasm.

2. Tumour Markers - The serum tumor markers include cancer antigen 125(CA 125), CEA (carcinoembryonic antigen) and CA19-9, AFP (alpha fetoprotein), serum beta hCG and LDH should be done in women less than 40 years of age with an ovarian mass, where suspicion of Germ cell tumor is high. Serum Inhibin may be done when Sex cord stromal tumor of the ovary is suspected or diagnosed.

CA125: This cancer antigen is the most common tumor marker evaluated in patients with suspected epithelial ovarian neoplasm. However, CA125 is a nonspecific marker, and is found to be elevated in many non-

gynecologic conditions and other benign gynaecological conditions like endometriosis and tuberculosis. It is recommended that serum CA125 should be measured in all postmenopausal women with an adnexal mass. The cutoff value in postmenopausal women is >35U/ml. However, in premenopausal women, it is recommended to measure a serum CA125 only if, the ultrasound appearance of a mass raises sufficient suspicion of malignancy to warrant a repeat ultrasound or surgical evaluation. The studies have shown that using a cut off value of CA125 >200U/ml, approximately 70 to 79% of premenopausal and 93 to 94% of postmenopausal patients with ovarian cancer will be captured by this threshold.

A very high level of CA 125 tumor marker is suggestive of epithelial ovarian cancer and a baseline value is useful in monitoring patients who are subsequently diagnosed with epithelial ovarian cancer. It is important to note that in approximately one half of patients with stage 1 epithelial ovarian neoplasm, the CA125 levels may be normal.

Risk of Malignancy Indices (RMI) - Several parameters like age, menopausal status, ultrasound findings are combined to provide risk of malignancy index in a woman. It is an index that helps to predict the probability of malignancy in a particular patient. With a cutoff level of 200, the sensitivity is 78% with specificity of 87%. A woman with RMI 1 score>250 should be referred to gynecologic oncologist.

RMI 1 Score: Ultrasound score x Menopausal status x CA125 level

Feature	RMI 1 score
Ultrasonography	0=none
Multilocular cyst Solid areas Bilateral masses Ascites Intraabdominal metastases	1=one abnormality 3=2 or more abnormalities
Premenopausal	1
Postmenopausal	3
CA125(U/ml)	

The following are the ACOG guidelines for referral of women with a pelvic mass to a gynecologic oncologist :

Premenopausal Women (Refer if Any are Present)

1. Very high CA125 levels*
2. Ascites
3. Evidence of abdominal or distant metastases

Postmenopausal Women (Refer if Any are Present)

- Elevated CA125 level
- Ascites
- Nodular or fixed pelvic mass

- Evidence of abdominal or distant metastases

Staging of CA Ovary - It is a surgicopathological staging which is finalised after surgery and histopathology

Stage IA: Tumor limited to 1 ovary (capsule intact) or fallopian tube; no tumor on ovarian or fallopian tube surface; no malignant cells in the ascites or peritoneal washings

IB: Tumor limited to both ovaries (capsules intact) or fallopian tubes; no tumor on ovarian or fallopian tube surface; no malignant cells in the ascites or peritoneal washings

IC: Tumor limited to 1 or both ovaries or fallopian tubes, with any of the following:

IC1: Surgical spill

IC2: Capsule ruptured before surgery or tumor on ovarian or fallopian tube surface

IC3: Malignant cells in the ascites or peritoneal washings

Stage II: Tumor involves 1 or both ovaries or fallopian tubes with pelvic extension (below pelvic brim) or peritoneal cancer

IIA: Extension and/or implants on uterus and/or fallopian tubes and/or ovaries

IIB: Extension to other pelvic intraperitoneal tissues

Stage III: Tumor involves 1 or both ovaries or fallopian tubes, or peritoneal cancer, with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes

IIIA1: Positive retroperitoneal lymph nodes only (cytologically or histologically proven):

IIIA1(i) Metastasis up to 10 mm in greatest dimension

IIIA1(ii) Metastasis more than 10 mm in greatest dimension

IIIA2: Microscopic extrapelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes

IIIB: Macroscopic peritoneal metastasis beyond the pelvis up to 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes

IIIC: Macroscopic peritoneal metastasis beyond the pelvis more than 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes (includes extension of tumor to capsule of liver and spleen without parenchymal involvement of either organ)

Stage IV: Distant metastasis excluding peritoneal metastases

Stage IVA: Pleural effusion with positive cytology

Stage IVB: Parenchymal metastases and metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)

Author: Prof. Nisha Singh

According to FIGO 2014 staging of ovarian cancer and NCCN guidelines for management of ovarian cancer, patients can be treated by two approaches:

1. Primary surgery (staging laparotomy/ primary debulking surgery) followed by adjuvant chemotherapy.

2. Neo-adjuvant chemotherapy followed by interval debulking surgery followed by adjuvant chemotherapy

Treatment Protocols for Epithelial Ovarian Cancer

FIGO stage	Primary Treatment	Adjuvant treatment
Stage **I (fertility desired)**	IA- Unilateral Salpingo-oophorectomy + comprehensive surgical staging IB -Bilateral Salpingo-oophorectomy + comprehensive surgical staging	Grade I(low grade) serous/endometroid: Observe Grade II: Observe or Chemotherapy x 3-6 cycles Grade III (high grade): Chemotherapy x 3-6 cycles
Stage **IA-IV (Surgical candidate, fertility not desired)**	Laprotomy/TAH/BSO +comprehensive surgical staging and debulking as needed	IC(Grade1,2 or 3): Taxane/Carboplatin x 3-6 cycles II,III,IV: Chemotherapy- a) Intraperitoneal chemotherapy in <1 cm optimally debulked Stage II and III OR b) Chemotherapy x 6 cycles - Completion surgery as indicated by tumor response and resectability in selected patients
Bulky stage III-IV or poor surgical candidate	Neoadjuvant chemotherapy ± interval debulking surgery(IDS)	Chemotherapy (total 6 cycles including neoadjuvant chemotherapy cycles)

Treatment protocols for Non Epithelial Ovarian cancer

Histological Type	Surgical Treatment	Adjuvant treatment
Dysgerminoma	USO staging if possible	BEP x 3 cycles if stage II-IV
Endodermal sinus tumor	Debulk but preserve fertility	BEP x 3-4 cycles
Embryonal carcinoma	As above	BEP x 3-4 cycles
Malignant teratoma	As above	BEP or VACx 3-4 cycles
Granulosa cell tumor	USO if young o/w TAH/BSO	BEP x 3-4 cycles GnRH agonists for advanced ds.
Sertoli-leydig cell	As above	BEP or VACx 3-4 cycles

Principle of Surgery for Ovarian Cancer Confined to Ovary/Pelvis - Maximal cytoreduction of all pelvic disease and evaluation for occult disease in upper abdomen or retroperitoneal lymph nodes.

Steps of Surgery

- Midline vertical incision is given
- Aspiration of ascitic fluid / peritoneal lavage for cytology
- Systematic evaluation of all peritoneal surfaces
- Palpation of all abdominal organs in clockwise manner (starting from right iliac fossa)
- Biopsy of adhesions/suspicious lesions
- Random peritoneal biopsies (paracolic gutters, pouch of Douglas and under surface of diaphragm)
- Hysterectomy with bilateral salpingo-oophorectomy with omentectomy in all cases (unilateral salpingo-oophorectomyin women desiring pregnancy)

- Pelvic and para-aortic lymphadenectomy.

Surgery for Ovarian Cancer Involving Pelvis And Upper Abdomen

- Cytoreduction of all abdominal, pelvic, and retroperitoneal disease, maximal effort to remove all gross disease as it offers superior survival.
- Total omentectomy
- Suspicious or enlarged lymph nodes are removed.

Chemotherapy Regimens

Epithelial Ovarian Cancer

a) 3 weekly paclitaxel (175 mg/m2)and carboplatin (AUC 5-6)

b) weekly Paclitaxel (80 mg/m2) and Carboplatin (AUC 5-6)

Non Epithelial Ovarian Cancer

They are treated with 3-4 cycles of BEP (Bleomycin, Etoposide, Cisplatin).

Follow Up of Treated Cases

It is done 3 monthly for first 2 years, 6 monthly for next 3 years and then annually life time.

Follow up is done with history, physical examination, and CA 125 levels.

If history/ examination findings are suggestive of recurrence or rising CA 125 levels, USG/CECT whole abdomen, pelvis and chest/ PET-CT whole body is advised.

Section

6

Gestational Trophoblastic Diseases

1. Complete H Mole and Partial H Mole
2. Gestational Trophoblastic Neoplasia

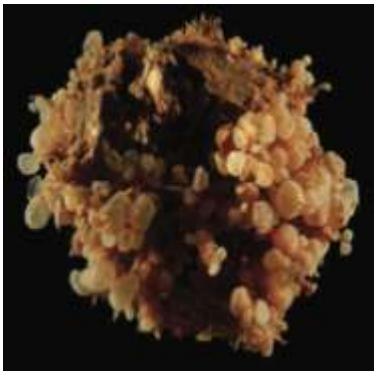

Fig 4- Molar Pregnancy

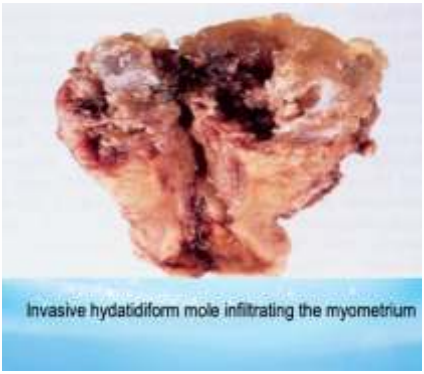

Fig 5- Invasive Mole

Author: Dr. Suchi Agarwal

Introduction

Gestational trophoblastic disease (GTD) is the term used to describe the heterogeneous group of interrelated lesions that arise from abnormal proliferation of placental trophoblast.

GTN refers to Gestational Trophoblastic Neoplasia which includes the malignant diseases related to gestational trophoblast. Although GTNs commonly follow a molar pregnancy, they can occur after any gestational event, including induced or spontaneous abortion, ectopic pregnancy, or term pregnancy.

Classification of GTD

Benign - Hydatidiform mole or vesicular mole

- Complete mole (CHM)
- Partial Mole (PHM)

Malignant

- Choriocarcinoma.
- Invasive mole
- Placental site trophoblastic tumor (PSTT).
- Epithelioid trophoblastic tumor (ETT).

Complete H. Mole

Symptoms

Amenorrhoea, vaginal bleeding and abdominal pain is present in 70% cases. The passage of vesicles is rarely observed except when the woman is aborting. Hyperemesis is reported in about 30% cases. Pregnancy induced hypertension (PIH) before 24 weeks is noted in

one-third of the cases. Thyrotoxicosis resulting in supraventricular tachycardia, dyspnoea and raised T_3 and T_4 levels is seen in 3% cases and is due to the fact that subunits of both thyroid-stimulating hormone (TSH) and hCG share a similar structure. One per cent women are asymptomatic and the condition is suspected by palpating an undue enlarged uterus.

Signs - The uterus feels doughy in consistency due to the absence of amniotic fluid. External and internal ballottement cannot be elicited and the fetal heart cannot be heard on the Doppler. Bilateral ovarian (Theca lutein) cysts may be present.

80% of hydatidiform moles resolve by treatment, 15%-20% may develop post molar GTN or invasive mole and 5% develop into choriocarcinoma.

Differential Diagnosis - partial mole, hydropic abortion and early nonmolar gestation with florid trophoblastic hyperplasia.

A Partial Mole (PHM) often presents with oligohydramnios, intrauterine growth retarded fetus or malformed fetus as detected on ultrasound scanning, during the second trimester. Few vesicles may be revealed in the placenta on ultrasound. A partial mole has a very low malignant potential (0-5%).

Complications - Hyperemesis gravidarum, pregnancy-induced hypertension, Haemorrhage, anaemia, Infection, Thyroid storm, Embolization with acute pulmonary insufficiency and coagulation failure.

Uterine perforation — spontaneous but more commonly during suction evacuation.

Delayed complications — Recurrent mole and chorio carcinoma

Diagnostic Modalities

Ultrasound -Ultrasound examination shows the 'snow storm' appearance in the uterus and the absence of fetal shadow in a complete molar pregnancy. Partial mole shows an ill formed fetus or few fetal parts with snow storm appearance in the placenta

Serumβ HCG – High level of Serum B-HCG significantly more than period of gestation.

Treatment

When a woman comes in the process of abortion, vesicles can be identified amongst the products passed. Blood should be transfused if required and intravenous oxytocin drip of 10–20 units or more in 500 mL of 5% glucose should be set up. Surgical evacuation with a suction evacuation machine (as in medical termination of pregnancy (MTP)), using No. 12–14 cannula reduces the blood loss. Tissue must be sent for histopathological evaluation.

Follow-Up for CHM or PHM

Normally, theβ HCG levels becomes negative in about 6–8 weeks following evacuation of a molar pregnancy. Weekly β HCG is recommended till negative. Once the test becomes negative, the patient is followed up monthly for 6 months.

Contraception-Pregnancy should be avoided for at least 1 year as a fresh pregnancy would interfere with the hCG levels. Barrier contraception or Combined oral pills can be offered. Intrauterine device and progestogen-only pills cause irregular bleeding and are best avoided.

Author: Dr. Shuchi Agarwal

Introduction

Gestational trophoblastic neoplasia is the malignant component of GTD and requires close attention in terms of recognition and diagnosis. It is commonly missed due to lack of knowledge by physicians treating abortions, ectopic and molar pregnancies. This is particularly so with missed abortions.

Any case of incomplete abortion or missed abortion that not respond to one uterine evacuation should be thoroughly investigated to rule out GTN before going for repeated evacuations.

Postmolar GTN

FIGO 2018 Criterion for Diagnosis of Postmolar GTN

A plateau (+/- 10%) in hCG levels over at least 3 weeks (i.e. 4 consecutive values);

A rise (≥ 10%) in hCG levels over at least 2 weeks (i.e. 3 consecutive values);

Histologic evidence of choriocarcinoma

Invasive Mole About 5–10% are invasive moles that erode the wall of the uterus, burrow into the myometrium and may cause dangerous internal haemorrhage. They behave as locally malignant leisons.

Choriocarcinoma This is a metastatic disease with high HCG levels. The histological examination shows all types of trophoblastic tissue but no chorionic villi.

Trophoblastic tumour following a full-term pregnancy is always choriocarcinoma, whereas it may be either an

invasive mole or a choriocarcinoma if it follows an abortion or a molar pregnancy. Trophoblastic tumour diagnosed up to 6 months following an abortion or a mole is often an invasive mole, but tumour diagnosed later than 6 months is usually a choriocarcinoma..

Placental Site Trophoblastic Tumour (PSTT)

About 1% of all trophoblastic diseases arises from the placental bed trophoblast and invades the myometrium. It follows a full-term normal delivery in 95%, though in rare cases, one follows a mole (5%). hCG levels are lower than that observed in choriocarcinoma, and rarely exceed 2000– 3000 IU/L. In contrast to other trophoblastic tumors, placental-site tumors are relatively insensitive to chemotherapy hence treated surgically or with radiation.

Metastatic Disease

The most common sites of metastases are lung (80%), vagina (30%), pelvis (20%), liver (10%), and brain (10%).

At the time of diagnosis, lung involvement is visible by chest radiography in 80% of patients with metastatic GTN. Patients with pulmonary metastasis may have chest pain, cough, hemoptysis, dyspnea, or an asymptomatic lesion visible by chest radiography. Respiratory symptoms may be acute or chronic, persisting over many months

FIGO Staging System for GTN

Stage I: Tumor confined to the uterine corpus.

Stage II: Metastases to the genital tract.

Stage III: Pulmonary metastases with or without uterine, vaginal, or pelvic involvement. The diagnosis is based on a rising hCG level in the presence of pulmonary lesions

viewed by chest radiography.

Stage IV: Advanced disease with involvement of the brain, liver, kidneys, or gastrointestinal tract.

WHO Risk Scoring System - for risk assessment

	0	1	2	4
Age (years)	≤39	>39		
Antecedent pregnancy	Hydatidiform mole	Abortion	Term	
Interval between end of antecedent pregnancy and start of chemotherapy (months)	<4	4–6	7–12	>12
Human chorionic gonadotropin (IU/L)	$<10^3$	10^3–10^4	10^4–10^5	$>10^5$
ABO groups		O or A	B or AB	
Largest tumor, including uterine (cm)	<3	3–5	>5	
Site of metastases		Spleen, kidney	GI tract	Brain, Liver
Number of metastases		1–3	4–8	>8
Prior chemotherapy			1 drug	≥2 drugs

*The total score for a patient is obtained by adding the individual scores for each prognostic factor. Total score: <7, low risk; ≥7, high risk.

Diagnostic Evaluation

- Determination of baseline hemoglobin, white blood cell and platelet counts
- Measurement of the serum hCG level Hepatic, thyroid, and renal function tests Chest radiograph or computed tomography (CT) scan
- Ultrasonography or CT scan of the abdomen and pelvis

Treatment of GTN

Single-agent chemotherapy is the preferred treatment in patients with low risk disease (Stage I). Low-risk disease

treated with primary single-agent chemotherapy has a high (approximately 80%) rate of remission.

Single-Agent Treatment Regimens

Box 3 First-line single agent chemotherapy regimens for low-risk gestational trophoblastic neoplasia

- MTX-FA 8-day regimen (50 mg MTX intramuscularly on days 1, 3, 5, 7 with folinic acid 15 mg orally 24 h after MTX on days 2, 4, 6, 8); repeat every 2 weeks.
- MTX 0.4 mg/kg (max. 25 mg) intravenously or intramuscularly for 5 days every 2 weeks.
- Actinomycin D pulse 1.25 mg/m^2 intravenously every 2 weeks.
- Actinomycin D 0.5 mg intravenously for 5 days every 2 weeks.
- Others: MTX 30–50 mg/m^2 intramuscularly weekly, MTX 300 mg/m^2 infusion every 2 weeks.

Abbreviation: MTX-FA, methotrexate–folinic acid.

When the disease is resistant to single-agent chemotherapy, combination chemotherapy should be administered.

All patients with High-Risk GTN (stages II–IV) should be treated with primary intensive combination chemotherapy and the selective use of radiation therapy and surgery with primary intensive combination chemotherapy

The EMA-CO regimen is the preferred primary treatment in patients with metastasis and a high-risk prognostic score (above 6). The drugs included are Etopside, Methotrexate, Actinomycin D, Cyclophosphamide and Vincristine.

Patients resistant to EMA-CO can be treated successfully by substituting etoposide and cisplatin on day 8 (EMA-EP).

Pregnancy should be avoided for 1 year after treatment completion.

Follow-Up of Patients with GTN

Low risk GTN - weekly measurement of hCG levels until they are normal for 3 consecutive weeks followed by monthly measurement of hCG values until levels are normal for 12 consecutive months. Effective contraception during the entire interval of hormonal follow-up.

High Risk GTN - weekly determination of hCG levels until they are normal for 3 consecutive weeks followed by monthly determination of hCG levels until they are normal for 24 consecutive months. The hCG regression curve serves as the primary basis for determining the need for additional treatment.

Section

7

Post Treatment Surveillance

1. Importance of Post treatment Surveillance in all Cancers

Author: Prof. Nisha Singh

Introduction

gynaecological cancers are an important public health issue as there is an increase in incidence of these cancers. Due to the lack of cancer awareness, variable pathology, and dearth of proper screening facilities in developing countries such as India, most women report in advanced stages to health care facilities. This adversely affects the prognosis, clinical outcomes, and follow-up.

Definition

Post treatment Surveillance or follow up of the gynaecological cancer patients refers to their evaluation after completion of treatment with a purpose to detect recurrence and treat it in a timely manner. Another purpose it to take care of their psychosocial, sexual and fertility needs. This is also of utmost importance to document overall and disease free survival outcome of the disease.

Traditional Versus Novel Approaches

Traditional follow-up programs fail to accommodate the patient's need for psychosocial and sexual supportive care and to actively involve patients and their relatives in the follow-up process. Individualised programs may replace traditional routine follow-up with fixed intervals and length. Focus on alarming symptoms and self-reporting may ensure detection of recurrence while allowing continuous attention to the patient's well-being and return to routine daily activities. Open communication is a very important step towards greater awareness of symptoms and early diagnosis of recurrence.

Physician Based Versus Nurse Led Surveillance

Different models of individual tailored and need-based follow-up have been tested. Nurse-led models have been tested against physician-led, face-to- face models versus telephone or virtual contacts and other models focusing on improving self-management, empowerment, or self-care against traditional follow-up. Both nurse and general practitioner facilitated followup have shown equal survival and quality of life levels when compared to traditional follow up and seem to provide a safe and stable environment.

Specifically, nurse led follow up may facilitate coherency and compliance of vulnerable patients, optimize involvement of both patients and relatives, and provide a holistic approach to unmet supportive care needs. Furthermore, it has shown similar or improved patient satisfaction when compared to conventional physician led follow-up.

Physical Versus Digital Surveillance

Models based on digital contacts have been compared to usual face-to-face contacts in hospital outpatient settings. The video or telephone-based contacts have most often been carried out by specialist nurses. Telephone-based follow-up has been described as a feasible, safe, and convenient high-quality alternative. It provides patients with a sense of confidentiality and seems to be more efficient as compared to face to face contacts.

Various electronic patient-reported outcome measures (ePROMs) or PROMs (patient-reported outcome measures) have been developed and tested for the purpose of adequately addressing and monitoring cancer patients' unmet needs. Additionally, PROMs are used for

the planning of frequency, content, specialist level, etc., of follow-up consultations in order to further individualize the follow-up program.

In a systematic review, use of PROMs was shown to improve patient-provider communication, treatment response, and patient satisfaction. In selected populations, the use of PROMS has demonstrated improvement in the quality of life, reduction in emergency room visits and hospitalizations, and improvement in quality-adjusted survival. For those reasons, PROMs are suggested as important elements of future follow-up programs for cancer patients.

Surveillance Protocols

Cervical Cancer - The median time to recurrence ranges from 7 to 36 months after primary treatment. History and physical examination is recommended every 3 to6 months for 2 years, every 6 to 12 months for another 3 to 5 years, andthen annually. Patients with high-risk disease can be assessed more frequently (eg, every 3 months for the first 2 years).

Endometrial Cancer - Most (65%–85%) recurrences are diagnosed within 3 years of primary treatment, and 40% of recurrences are local. Follow-up is recommended every 3-4 months for 2-3yrs, then every 6 months and then annually after 5 years.

Ovarian Cancer - Surveillance with symptoms, physical examination and CA-125 is recommended every 3 monthly for first 2 years, 6 monthly for next 3 years followed by annually lifetime.

Gestational Trophoblastic Neoplasia- Follow-up with βHCG levels every month for 12 months is recommended for surveillance. Reliable contraception must be used throughout this period. Future fertility and pregnancy are not affected but psychosocial and sexual counseling may be needed for patients.

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