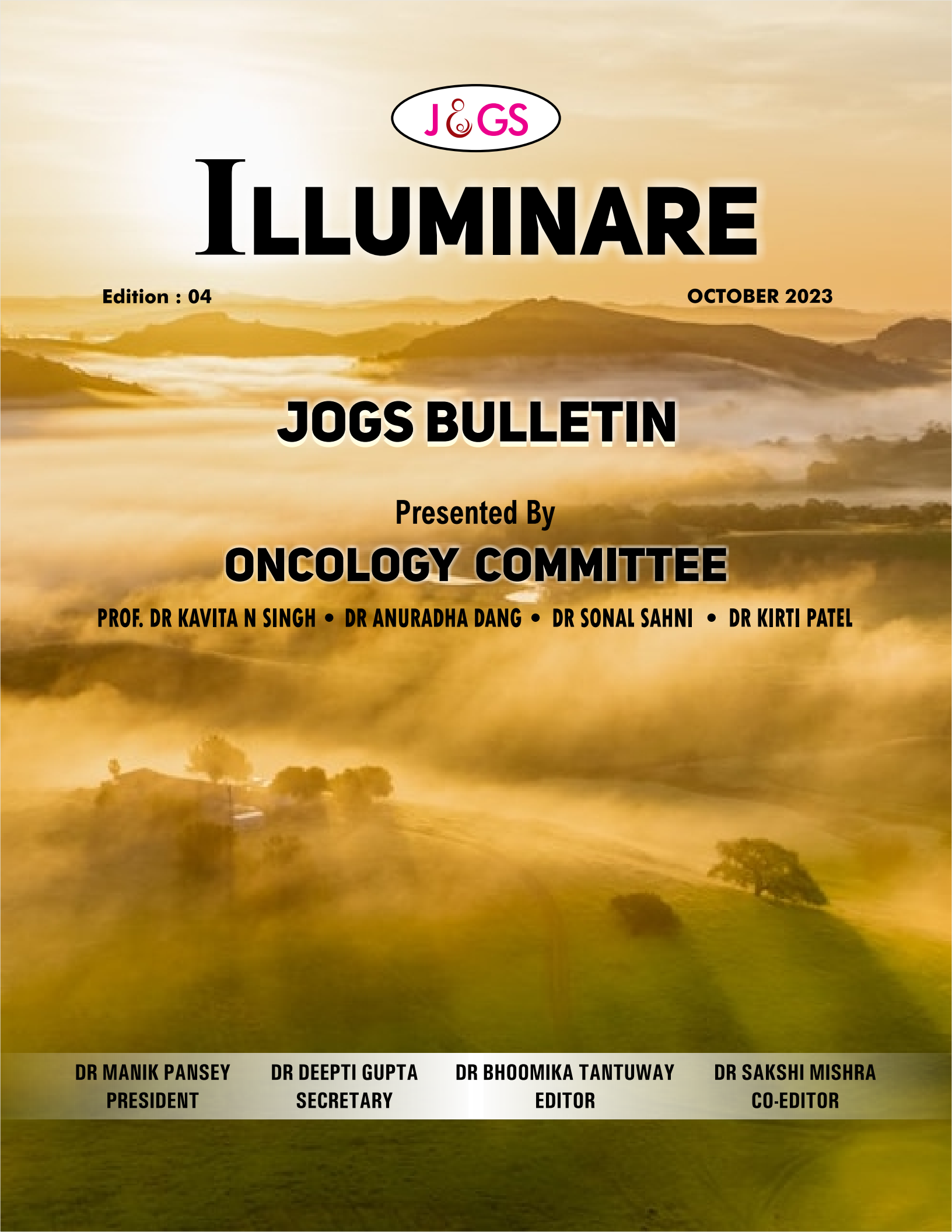


J&GS

ILLUMINARE

Edition : 04

OCTOBER 2023

JOGS BULLETIN

Presented By

ONCOLOGY COMMITTEE

PROF. DR KAVITA N SINGH • DR ANURADHA DANG • DR SONAL SAHNI • DR KIRTI PATEL

EDITORIAL

DR MANIK PANSEY
President - JOGS

DR DEEPTI GUPTA
Secretary - JOGS

DR BHOOMIKA TANTUWAY
Editor - JOGS

DR SAKSHI MISHRA
Co-Editor - JOGS

Hello every one

"There is no medicine like hope, no incentive so great and no tonic so powerful as expectation of something better tomorrow."

This edition covers basket of all the topics of Preventive oncology from all the eminent experts around the country. The incidence of Cancer among women is rising day by day and all form of Cancers like Ca Breast, Ca Ovary, Ca Cervix, Ca Endomelium are at rise in our country also.

This Bulletin aims to discuss the Molecular Markers of Cervical Cancer, Role of Laparoscopy in Malignancy, Recent Advances in Ovarian Cancers along with highlights on Fertility Preservation in Malignancy.

It is said that cancer is only going to be a chapter in your life, not the whole story.

With this thought in our mind for cancer prevention and treatment, let's join our hands on **"THE ROAD TO CURE."**

Even if one cancer is prevented and one cancer is cured, its is worth a million.

Happy Reading
Stay Fit, Fine and Healthy.
Thank You !

JOGS GYNAE-ONCOLOGY COMMITTEE

PROF. DR KAVITA N SINGH

DR ANURADHA DANG

DR SONAL SAHNI

DR KIRTI PATEL

Dear Friends,

Greetings from the team JOGS Oncology Committee & AGOI- MP State Chapter.

"Education is key to unlocking the world, a passport to freedom."

Foremost,a big applause to all fraternity members of Jabalpur Obstetrics & Gynaecology society on winning the coveted FOGSI Presidents Rotating Trophy 2022-23. The sheer dedication and relentless hardwork of all society members has shaped this victory.

Another feather in our cap is FOGSI Dr Duru Shah Distinguished Community Service Award 2022 to Professor Dr Kavita N Singh. She has dedicated her life in the service of women health and her unprecedented efforts have placed Jabalpur on the global map of cancer prevention as a WHO Master Trainer Colposcopy.

Our motto is "Team work makes the dream work". Keeping in mind the Millenium Development Goals WHO 2030 as our guiding principle,we intend to conduct sociala wareness campaigns in and around Mahakaushal area and reach out to the masses with cancer prevention, early detection and treatment options. We plan to organize continuous medical education programs and upgrade our skills & knowledge regarding latest technologies in oncology.

We plan to sow the seeds of interest in preventive and operative oncology so that the burden of cancer in our society declines in future. We will invite and involve eminent speakers and trainers from across the country to enhance the technical expertise of generation-next gynaecologists.

Bench marks have been set by our extremely efficient predecessors and we will strive hard to prove ourselves worthy of this heritage. We hope to make our tenure at AGOI-MP State Chapter as a truly learning, interactive, enriching, enjoyable academic and social experience.

The take home message is to spread a word of awareness to all.

"Get Vaccinated, Get Informed, Get Screened, Get Treated"
Thank You !

FERTILITY PRESERVATION IN CANCER PATIENTS

Dr. Seema Singhal
Additional Professor
Department of Obstetrics and Gynaecology, AIIMS Delhi

" The quality of life is more important than life itself"

With increasing incidence of cancer in reproductive age, and availability of newer treatment modalities, the number of young cancer survivors is on the rise.(1). The number of cancer cases in India is projected to go up from 14.6 lakh in 2022 to 15.7 lakh in 2025. Chemotherapy and Radiotherapy adversely affect fertility in males and females. DNA damage in oocytes has mutagenic and teratogenic effects. Ovulatory dysfunction postchemotherapy is quite common especially with the use of alkylating agents. There is fibrosis and endometrial atrophy postradiotherapy due to compromised bloodflow to the endometrium. There is increased risk of miscarriage, IUGR, pretem birth, LBW and infertility. In males, Chemotherapy has deleterious effects on seminiferous tubules a well. Fertility preservation is defined as the use of available technologies to help indivisuals retain their fertility / ability to procreate. Fertility preservation is a big step in improving quality of life of such patients.

For best outcome, fertility Preservation should be done before starting treatment for cancer. If not done before cancer therapy, it should be done 6 months post treatment.(2).The optimal timing of conception after cancer treatment is uncertain but some suggest at least waiting period of six months after chemotherapy and 12 months after radiotherapy considering the half-life of treatments and the duration of time for oocyte maturation.

The techniques available are-

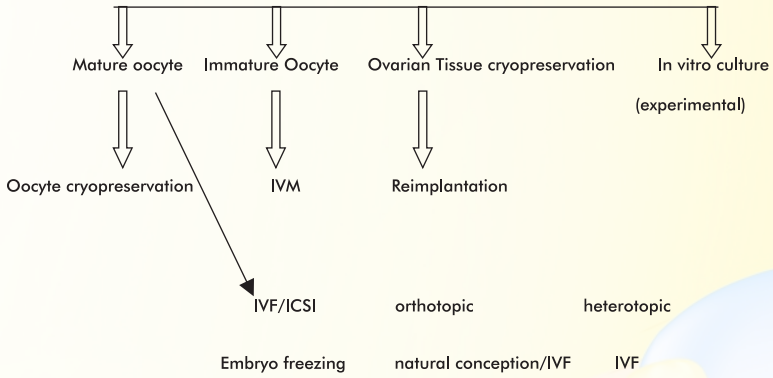
A. Surgical Techniques

1.	Oophropexy	Ovarian transposition done surgically just before radiotherapy to get ovaries out of the radiation field. Most common location is above the pelvic brim. Success rate overall is around 50% and complications include ovarian cyst formation, chronic pelvic pain, postop adhesions, pain, migration back into ovarian fossa, premature ovarian failure, OPU may not be feasible through vaginal route; needing abdominal approach.
2.	Radical Trachelectomy	Can be done for Ca cervix pts with early stage disease < 2cm. Complications are risk of cervical incompetence, preterm birth, LBW. Xu et al conducted a study which reported that in patients with early stage cervical cancer there was no significant difference in recurrence, mortality, survival when compared to radical hysterectomy.
3.	Unilateral oophorectomy/ cystectomy	Can be considered in cancers that are slow-growing and less likelyto spread, like borderline, low malignant potential, germ cell tumors, or stromal cell tumors (typically Grade 1 and some Grade 2 epithelial ovarian cancers). Such patients have to be followed up vigilantly as the recurrence in such cases is high. In a study on the same by Kajiyama it was shown that there was no difference in the 5 year survival and even the disease free survival on comparing with Total hysterectomy with bilateral salpingo-oophrectomy.

B. Medical and Conservative management

1.	Progesterone Therapy	Patients with a early stage well differentiated endometrial cancer can be offered progestogens. Two thirds of these respond very well to such treatments, with acceptable pregnancy and live birth rates. Like in the case of ovarian tumours vigilant followup is necessary as recurrence rate is around 18-40%.(3).
2.	Gonadal Shielding during radiotherapy	Useful in selected cases only.
3.	Fertility protective agents	GnRH analogues and Antagonists: They are given along with and before chemotherapy treatment. Benefit of these treatments are controversial. GnRH agonists and oral contraceptives have been used to preserve fertility in advanced cases of Hodgkin lymphoma.
4.	Expectant management	Waiting for 6 months to 2 years after chemotherapy will help recover gamete quality and number. It also reduces risk of birth defects dues to damaged gametes. The 2-year period is generally based on the fact that recurrence is usually highest in the first 2 years after treatment. But women who have had chemo or radiation to the pelvis are also at risk for sudden early menopause even after they start having menstrual cycles again. Menopause may start 5 to 20 years earlier than expected.
5.	Adoption	Most adoption agencies state that they do not rule out cancer survivors as potential parents. But agencies often require a letter from the doctor stating that one is cancer-free and can expect a healthy life span and a good quality of life. Some agencies or countries require a period of being off treatment and cancer-free (average of 5 yrs) before a cancer survivor can apply for adoption.

Schematic Representation of fertility Preservation Techniques using ART.



C. Assisted Reproductive Techniques

1.	Assisted reproductive Techniques	IUI, IVF, ICSI can be helpful. But there are very rare studies that have analyzed results after ART treatment in cancer survivors. Third party reproduction using Donor egg/ embryos/ sperms/ surrogacy can be useful in some cases. Rules ans regulations published in ART act and Surrogacy act should be followed.
2.	Embryo Cryopreservation	It is the treatment of choice in married women or those with a committed partner, has good success rates. Drawbacks are that ovarian stimulation may take upto 2 weeks,delaying the cancer treatment and supraphysiologic estradiol levels during stimulation which may negatively affect estrogen sensitive cancers predisposing to relapse.(4). There is increased risk of anesthesia related complications during OPU. Side effects like OHSS and thromboembolic complications can be life threatening in these patients. The procedure cannot be offered to prepubertal girls. Also, a limited number of oocytes can be harvested in one attempt, limiting the number of attempts for pregnancy. Data regarding the success of embryo cryopreservation in cancer patients is scarce.

3.	Oocyte cryopreservation	It is a established technique especially for unmarried women. It is considered a better option for all women as it helps them maintain their reproductive autonomy. Data regarding the success rates of this technique in cancer patients is again limited and success rates extrapolated from oocyte donors is used to counsel the patients.
4.	Ovarian Tissue Cryopreservation	The procedure consists of surgically retrieving and then freezing ovarian tissue (cryopreservation of small pieces of ovarian cortex) and later transplanting it back to the body. After cryopreservation, cancer treatment can be started. Ovarian tissue reimplantation should be planned once the patient is in remission and is ready to conceive or starts experiencing symptoms of ovarian insufficiency as these grafts are known to have limited lifespan. Ovarian function is known to resume after 60-240 days of reimplantation .(5). Ovarian tissue can be transplanted in the pelvis (orthotopic transplantation) or subcutaneously in the abdomen or forearms (heterotopic transplantation). Orthotopic transplants are more successful than heterotopic transplants and many spontaneous successful pregnancies have been reported following orthotropic reimplantation of ovarian tissue.. IVF is must with heterotopic implants. Reimplantation should be a team approach and the oncologist and perinatologist should be consulted and potential obstetric and perinatal complications should be discussed. Compared to the other techniques it has the advantages of saving large number of oocytes and may allow for spontaneous pregnancy after treatment without the need of ART or ovarian stimulation. It also does not delay the start of cancer treatment. This is the only method of fertility preservation in prepubertal girls and the preferred choice for unmarried women. Drawbacks are that OTC requires a surgical procedure which may have anaesthesia related risks in women with cancer due to associated comorbidities. Another very significant concern may be the possibility of contamination of ovarian tissue by malignant cells. Cryopreserving ovarian tissue may prevent thorough pathologic examination of the ovaries and, therefore, miss an occult epithelial malignancy so, orthotopic transplantation should not be done in cases where occult malignancies cannot be ruled out. Other risks of OTC are occasionally risk of graft failure and compromised oocyte quality with lower than expected fertility rates even with IVF. Orthotopic ovarian transplantation should be deferred in women at high risk of ovarian metastasis and alternative procedures like in vitro follicle growth and oocyte maturation should be offered. Alternatively, the graft can be planted heterotopically and later removed after the child bearing.

Where there is a concern over the transmission of genetically linked cancers Preimplantation genetic diagnosis (PGD) is a technique, which can be offered to screen embryos for genetically transmissible diseases prior to implantation. In this era the counseling for patients specially those with good prognosis for long term survival should have a multidisciplinary counseling involving both oncologists and gynaecologists. Given the reproductive risks of cancer therapy and improved long term survival, there is a growing interest in expanding the reproductive options for cancer patientsFertility preservation techniques have indeed come a long way in improving quality of life of these patients.

REFERENCES

1. National Cancer Registry of India.
2. Noyes N, Melzer K, Druckenmiller S, Fino ME, Smith M, Knopman JM. Experiences in fertility preservation: Lessons learned to ensure that fertility and reproductive autonomy remain options for cancer survivors. J Assist Reprod Genet.2013;30:1263–70.
3. Dorais J, Dodson M, Calvert J, Mize B, Travarelli JM, Jasperson K, et al. Fertility-sparing management of endometrial adenocarcinoma. ObstetGynecolSurv. 2011;66:443–51.
4. Revelli A, Porcu E, Levi Setti PE, DellePiane L, Merlo DF, Anserini P. Is letrozole needed for controlled ovarian stimulation in patients with estrogen receptor-positive breast cancer? GynecolEndocrinol. 2013;29:993–6.
5. Morris SN, Ryley D. Fertility preservation: Nonsurgical and surgical options. SeminReprod Med. 2011;29:147–54.

MANAGEMENT OF CERVICAL INTRAEPITHELIAL NEOPLASIA - AN UPDATE

Dr. Nisha Singh

Incharge Genital Cancer Control Unit, Department of Obstetrics and Gynecology

King George's Medical University, Lucknow

Introduction

The worldwide annual incidence of cervical cancer is approximately 510,000 with approximately 288,000 deaths annually. It is estimated that there are around 132,000 new cases and 74,000 deaths per year in India that account 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 about 6-8%.

There has been a 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.

WHO call for elimination of cervical cancer

In 2020, the World Health Organization (WHO) launched the **90-70-90** strategy for cervical cancer elimination by 2030. This includes HPV vaccination of 90% of eligible girls by the age of 15 years, screening of 70% of women by high performance tests by 35-45 years of age and treatment of 90% of women with CIN or cervical cancer. Hence diagnosis and treatment of CIN is an important pillar for cervical cancer elimination.

What is CIN - The concept of CIN was given by Richart in 1968 [3]. It is an atypical proliferation of immature squamous epithelium with intact basement membrane. The pathological findings that define CIN are presence of immature cells, loss of polarity, increased nucleo cytoplasmic ratio, increased normal and abnormal mitotic figures, coarse chromatin and loss of normal cell differentiation. If these mitoses and immature cells are limited to lower one-third of epithelium, the lesion is called CIN1(LSIL in Bethesda system). Involvement of middle and upper third of epithelium is diagnosed as CIN2 and CIN 3(HSIL in Bethesda system) respectively.

Where does CIN develop - The squamocolumnar junction (SCJ) 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 phase and leads to the formation of the Transformation Zone (TZ) between original and new SCJ. [3] CIN develops in the TZ in response to persistent HPV infection.

There are three types of TZ:

- Type 1TZ: Both the original and new SCJ are located on the ectocervix and can be seen clearly.
- Type 2 TZ: The new SCJ is located either fully or partially within the endocervical canal and can be seen with or

without use of endocervical speculum.

- Type 3 TZ: The new SCJ is located within the endocervical canal and is only partially visible or not at all visible, even with an endocervical speculum

Etiology of CIN

Cervical cancer and CIN are caused by 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 and 30 of them are anogenital type. High risk lesions are mostly caused by HPV 16,18,31,33,35,39,45,51,58.

Most of the sexually active reproductive age women acquire HPV infection once in lifetime but 80% of them clear it through natural process. About 20% have persistent HPV infection that later leads to CIN or cervical cancer. The possible risk factors for persistent HPV infection are low socioeconomic status, poor menstrual hygiene, nutritional deficiencies, immunocompromised status, early age at first intercourse, multiple sexual partners, reproductive tract infections (RTI), Asian, African ethnicity, multi parity, smoking and oral contraceptive usage. Hence, primary prevention for CIN includes health education, barrier contraception, treatment of RTI and HPV vaccination.

Clinical presentation

Women may be completely asymptomatic or may present with vaginal itching, redness, dirty, foul smelling discharge or with bleeding during intercourse or cervical examination.

Screening for CIN

The three main screening modalities for CIN are HPV DNA test, Pap smear or LBC and VIA/ VILI. Screening frequency by using HPV test is as low as 5 yearly, due to its high sensitivity and negative predictive value. The specificity of Pap smear is very high (98%) but its sensitivity is low (50%). LBC removes any artifacts, allows better cytological assessment of basal, parabasal and superficial cells and the sample can also be used for HPV testing. VIA/ VILI are alternatives for community settings only in non availability of HPV test.

WHO 2021 Guidelines for cervical cancer screening

WHO guidelines include 23 recommendations and 7 good clinical practice statements. The major change is the recommendation for HPV DNA test as the primary screening modality. HPV DNA test should be used for screening all women between 30 to 50 years of age.

Under **SCREEN AND TREAT APPROACH**, screen positive women suitable for ablative procedure are treated and then followed up after 12 months. VIA test with 3-5% acetic acid is recommended for deciding eligibility for ablative procedure. Cases with obvious growth or suspected cancer should be biopsied and managed accordingly. Women with negative HPV test should be reassessed after 5-10 years while women living with HIV every 3-5 years. Negative VIA or cytology cases should be re-screened after 3 years.

Under **SCREEN TRIAGE AND TREAT APPROACH**, triage may be done with partial genotyping, colposcopy, VIA or cytology as feasible. Those positive for HPV 16/18 or VIA should be taken up for ablative or excisional procedure as per eligibility.

Colposcopy and Biopsy for confirmatory diagnosis of CIN

A colposcope is a binocular stereoscopic microscope capable of at least 16× magnification, it has a centre light with green filter.. Adjustable magnification, real-time video, still cameras, and ocular arms allow simultaneous examination by a student or preceptor. Colposcopy with targeted biopsy is the primary method of detecting precancers requiring treatment.

Abnormal colposcopic findings include acetowhite epithelium, punctation, leukoplakia, mosaicism, and atypical vessels. Reporting of colposcopy findings is done as per IFCPC- 2011 nomenclature [3]. The reporting is based on

Swede's score that has five characteristics (aceto uptake, margins, size, vessels and iodine uptake). Total score 0–4 correlates with normal/CIN1, 5–8 with CIN2/CIN3 and 9–10 correlates with CIN3/cancer.

Because patients are managed less aggressively after a colposcopic examination where CIN 2+ is not found, maximizing detection of CIN 2+ at each colposcopy visit is paramount. Biopsies should be taken of all discrete acetowhite areas, usually 2 to 4 biopsies at each colposcopic examination.

For those at lowest risk (less than HSIL cytology, no HPV 16/18 infection, and a completely normal colposcopic impression), untargeted (random) biopsies are not recommended. These guidelines apply to women and transgender men with a cervix, including those who have undergone supracervical hysterectomy.

Diagnostic excisional procedure should be done for inadequate colposcopy. Endocervical curettage is indicated for type 3 TZ and absence of lesion on the ectocervix with abnormal screening or when glandular abnormalities are suspected on cytology.

MANAGEMENT OF CERVICAL INTRAEPITHELIAL NEOPLASIA

The recent ASCCP (2019) recommendations for CIN management are based on risk of CIN3+ rather than result based. Risk calculations are as per past screening history, age, immunocompromised status and previous CIN treatment history. Other important changes include the following:

- Colposcopy can be deferred in conditions with low risk abnormalities (below 4%).
- Expedited treatment is (treatment without colposcopic biopsy) is recommended in high risk cases(risk above 25%).
- Excisional treatment is preferred to ablative treatment for histologic HSIL (CIN2/3) and recommended for AIS.
- Observation is preferred to treatment for CIN 1.
- HPE reporting of HSIL should include CIN 2/3 qualifiers based on LAST/WHO recommendations.
- All positive primary HPV screening tests, regardless of genotype, should have reflex triage testing performed to plan further management.

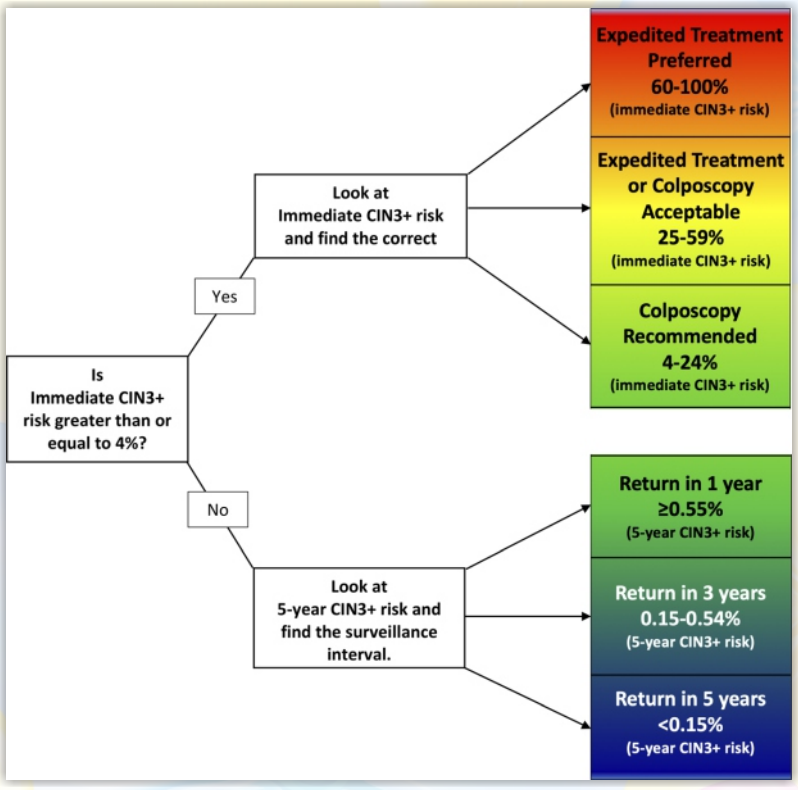


Figure 1 shows the risk based management plan (ASCCP 2019).

CIN Management in special situations

CIN1 on colposcopy / biopsy for women above 30 years

If the preceding HPV test was positive or cytology showed ASCUS / LSIL, it should be subjected to repeat screening at 1-2 yr, if negative, should return to routine follow up. If CIN1 persist for 2 yrs, ablative or excisional procedures should be done.

In case of preceding ASC-H or HSIL, diagnostic excisional procedure is preferred. Ablative treatment may be done for non compliant cases.

Management of women below 30 yrs desirous of pregnancy with CIN1 on histology

If the preceding cytology was ASCUS / LSIL, repeat screen at 1year. 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 1year, diagnostic excision should be done.

Management of CIN 2/3 in women desirous of pregnancy

For CIN3 with inadequate colposcopy, excision should be done. For CIN2, facility of p16 or Ki67 helps in taking decision. Active expectancy is an alternate for CIN 2 in women desirous of pregnancy. So colposcopy should be done at 6 months; if lesion persists, go for excision, or repeat cytology or colposcopy at 1 year. At any point, if high grade cytology is found or there is worsening of colposcopic findings, excision is recommended otherwise repeat cotesting after 1 year.

CIN in pregnancy - One must review colposcopy report, if colposcopy suggests 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.

TREATMENT MODALITIES FOR CIN

The basic principles of CIN treatment are as follows:

- The whole TZ should be excised or ablated irrespective of the size of the lesion as the entire TZ is at risk of developing CIN.
- Tissue destruction during ablative treatment must extend upto 7-8mm as the high grade CIN lesions often extend into crypts present in TZ upto 5mm. During excisional treatment, entire TZ including full length of crypts is removed.
- CIN 2 and 3 lesions should always be treated except in women below 25 years.
- The decision to treat the lesion may be based on colposcopic findings without waiting for histological verification. VIA or HPV positive cases may be treated without colposcopic or histological verification in community settings.

CRYOTHERAPY

This technique 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 drops to -60 to -80 °C, the tissue temperature is reduced to-20 °C, causing permanent damage to the epithelial cells. The ectocervix has sparse sensory nerve endings, hence cryotherapy does not require any anaesthesia.

Eligibility - It should be used to treat only those CIN1/CIN2/CIN3 lesions that are limited to ectocervix without any extension to the endocervix or to the vagina. The TZ should be type 1 and the lesion should occupy 75% of the cervix. Cryotherapy probe should cover the lesion and there should not be any suspicion of invasive cancer or glandular abnormality.

THERMAL ABLATION

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. Multiple applications are feasible with thermal coagulation. Hence, its use 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, it is known as "cold" coagulation. The rest of the principles and indications are same as those for cryotherapy. Thermal coagulation is as effective as cryotherapy in treating CIN lesions with the advantage of use of electricity and more recently battery

driven portable devices.

LEEP (Loop electrosurgical excision procedure)/LLETZ (Large loop excision of TZ)

They are one and the same and indicated in cases that are not suitable for ablation therapy with the 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 TZ and no visible lesion on colposcopy with persistently abnormal cytology. LEEP may also be performed for Cervical glandular intraepithelial neoplasia (CGIN), adenocarcinoma in situ (AIS) and micro invasive cancer where cold-knife conization is preferred.

COLD KNIFE CONIZATION

This is an excisional method of treating high-grade CIN where the cervical cone is removed without any energy device. This is recommended in case of AIS and micro invasive cancer. It can also be used in HSIL with type 3 TZ in settings where LLETZ facilities are not available.

The width and length of the cone depends 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 is that the margins are free of any thermal damage. The procedure is done under general or regional anaesthesia, needs skilled providers and has higher complication rates.

PERSISTENT or RESIDUAL DISEASE - Persistence of high grade lesion with no intervening documented absence of disease after initial treatment.

RECURRENT DISEASE - Detection of a histopathological high grade lesion on biopsy or a subsequent surgical specimen (hysterectomy, CKC and LLETZ) following a documented absence of high grade lesion at any time interval after the initial treatment was performed.

FOLLOW-UP TESTS

Follow up recommendations are same for general population and HIV positive women.

Follow up is must if a woman is treated with ablation or LLETZ based on histopathology or without histopathology. It should be done at 6 months with HPV test, if positive, should be retreated with LLETZ followed by retesting within 12 months. Annual surveillance for 3years is recommended after the test of cure at 6 months. Continued surveillance with HPV or cotest at 3-year is recommended for at least 25 years after initial post-treatment management of histologic HSIL, CIN 2, CIN 3, or AIS. New evidence indicates that risk remains elevated for at least 25 years, with no evidence that treated patients ever return to risk levels compatible with 5-year intervals.

Surveillance with cytology alone is acceptable only if HPV or cotest is not feasible. Cytology is less sensitive than HPV and is therefore recommended more often. Cytology at 6-month when HPV or cotest is recommended annually. Cytology annually when HPV is recommended at 3-year intervals.

Conclusion

Cervical Intraepithelial Neoplasia is the precursor of cervical cancer that can be easily screened and diagnosed. Timely treatment with ablative or excisional procedure will definitely help in eliminating cervical cancer.

References

1. Bruni L, albero G, Serrano B, et al. ico/iarc information centre on hpV and cancer (hpV information centre). human papillomavirus and related Diseases in the World. Summary report 22 october 2021. available from: https://hpvcentre.net/ statistics/reports/XWX.pdf
2. WHO guideline for cervical cancer screening and treatment of pre cancer lesion for prevention of cervical cancer-Second edition. 2021. available from https://www. who.int/ publications/i/item/9789240030824.
3. 2019 ASCCP Risk-Based Management Consensus Guidelines for Abnormal Cervical Cancer Screening Tests and Cancer Precursers. Journal of Lower Genital Tract Diseases. 2020, 24(2); 102-131.

MOLECULAR MARKERS IN CERVICAL CANCER

Dr. Harsha Mohanasundaram
DNBPG (OBGY)
GKNM Hospital, Coimbatore
Dr. Latha Balasubramani
GYNAE Oncologist
GKNM Hospital, Coimbatore

Introduction

Cancers of the cervix are the third most common cancer in the developing countries. Approximately 569,847 new cases of cervical cancer are diagnosed and 311,365 patients die of the disease every year worldwide.Early identification, diagnosis and treatment plays a vital role in management of cervical cancer. Cancer research more recently has focused on the use of molecular markers for precise diagnosis, to predict response to therapy and survival and in implementing the targeted therapies. However their routine use remains challenging in regular clinical practice.

Haematological Markers

Many haematological markers are identified to predict response to chemo-radiation therapy. Anemia is known to be associated with tumour hypoxia and neo-angiogenesis. Hemoglobin levels below 10 g/dL during RT have been shown to have an inferior disease-specific survival.

Cancer-related systemic inflammation is also associated with impaired outcomes in patients with malignant diseases.This includes tumour-induced neutrophilia, thrombocytosis and relative lymphocytopenia. Elevated pretreatment neutrophil to lymphocyte ratio may be used as an independent predictor of a decreased overall survival rate.

HPV

HPV DNA may also be a useful biomarker for locally advanced cervical cancer.

The integration of HPV into the host genome causes partial or complete deletion of the viral genes E1 and E2.The loss of E2 function leads to a more radio-resistant phenotype by potentiating E6 and E7 expression which are found to improve the radiosensitivity of HPV-positive cervical cancer cells by increasing the intrinsic radiation sensitivity.HPV 18 positive tumours are more aggressive and often result in impaired prognosis following radiotherapy.

Molecular protein markers

Tumour progression is induced and promoted by viral oncoproteins E5, E6 and E7 in HPV associated malignancies. Cervical cancer cells with specific PIK3CA-E545K mutation have been found to be more resistant to cisplatin or cisplatin-based concurrent RT. In cervical cancer, a high expression level of hypoxia-inducible factor 1 α (HIF-1α) is linked with poor prognosis and therapy resistance.

An over expression of COX-2 is frequently associated with angiogenesis, disease progression, metastatic behaviour and therapy resistance.As upstream modulators of COX-2, members of the mitogen-activated protein kinase (MAPK), extracellular-signal regulated kinase (ERK) family and EGFR may be indicators of outcome and survival in cervical cancer.Elevated levels of EGFR were associated with inferior OS and DFS. Moreover, EGFR overexpression was correlated with a higher incidence of lymph node metastases and tumor size.

PLK1 (protein kinase) is related to cellular proliferation and tumor growth. Its overexpression has been shown to have a negative impact on survival.

MicroRNA, Long-Non-Coding RNA and Circular RNA

Micro RNA (miRNA), long-non-coding RNA (lncRNA) and circular RNA (circRNA) encompass a variety of RNA molecules that are identified as potential dynamic biomarkers to predict therapeutic response and survival and may be useful for monitoring and detecting persistent or recurrent disease.

Circulating Tumour Cells (CTC), Circulating Cell-Free DNA (cfDNA) in Cervical Cancer

Recent advancements in technology has helped in detection of small amounts of RNA, DNA as well as tumour cells in a patient's peripheral blood which is a promising diagnostic, prognostic and dynamic tool.

Decrease in the CTC count is associated with a lower risk of death.

Higher ctDNAs levels are associated with advanced FIGO stage, tumour size, grading and lymph node metastases. Circulating miRNAs have also been studied with lower levels associated with a higher incidence of lymph node metastases, a higher tumour volume and adenocarcinomas.

Tumour Microenvironment (TME) in Cervical Cancer

A network of immune and endothelial cells, fibroblasts, signalling proteins and extracellular matrix molecules within the tumour and the surrounding tissue constitutes the TME. Thus, immunosuppressive and immunogenic tumour-infiltrating immune cells have a major role.

Immunohistochemical detection of CD3 (pan T-cell marker), CD4, CD8, CD20 (B-cells) CD206 (macrophages) revealed an association of CD8+ with pelvic lymph node metastases.

"Cold" malignancies were defined by a lack of CD8+ lymphocytes in the tumour and stroma and were associated with a significantly larger tumour volume and a worse DFS.

Conclusion

In conclusion, exact prediction of treatment response and survival will aid in targeted therapies thereby improving the treatment and survival.Identification of valid and reproducible biomarkers are essential to identify cellular processes that will help in better treatment strategies that will improve cancer outcomes.

References

1. Chesson H.W., Dunne E.F., Hariri S., Markowitz L.E. The Estimated Lifetime Probability of Acquiring Human Papillomavirus in the United States. Sex. Transm. Dis. 2014;41:660–664.
2. Koulis T.A., Kornaga E.N., Banerjee R., Phan T., Ghatage P., Magliocco A.M., Lees-Miller S.P., Doll C.M. Anemia, Leukocytosis and Thrombocytosis as Prognostic Factors in Patients with Cervical Cancer Treated with Radical Chemoradiotherapy: A Retrospective Cohort Study. Clin. Transl. Radiat. Oncol. 2017;4:51–56. doi: 10.1016/j.ctro.2017.05.001
3. Shinko D., Diakos C.I., Clarke S.J., Charles K.A. Cancer-Related Systemic Inflammation: The Challenges and Therapeutic Opportunities for Personalized Medicine. Clin. Pharmacol. Ther. 2017;102:599–610. doi: 10.1002/cpt.789.
4. Huang H., Liu Q., Zhu L., Zhang Y., Lu X., Wu Y., Liu L. Prognostic Value of Preoperative Systemic Immune-Inflammation Index in Patients with Cervical Cancer. Sci. Rep. 2019;9:3284. doi: 10.1038/s41598-019-39150-0.
5. Lindel K., Rieken S., Daffinger S., Weber K.J., de Villiers E.-M., Debus J. The Transcriptional Regulator Gene E2 of the Human Papillomavirus (HPV) 16 Influences the Radiosensitivity of Cervical Keratinocytes. Radiat. Oncol. 2012;7:187. doi: 10.1186/1748-717X-7-187
6. Fleischmann M, Chatzikonstantinou G, Fokas E, Wichmann J, Christiansen H, Strebhardt K, Rödel C, Tselis N, Rödel F. Molecular Markers to Predict Prognosis and Treatment Response in Uterine Cervical Cancer. Cancers (Basel). 2021 Nov 17;13(22):5748. doi: 10.3390/cancers13225748. PMID: 34830902; PMCID: PMC8616420.
7. Cafforio P., Palmirotta R., Lovero D., Cicinelli E., Cormio G., Silvestris E., Porta C., D'Oronzo S. Liquid Biopsy in Cervical Cancer: Hopes and Pitfalls. Cancers. 2021;13:3968. doi: 10.3390/cancers13163968.
8. Vasseur A., Kiavue N., Bidard F.-C., Pierga J.-Y., Cabel L. Clinical Utility of Circulating Tumor Cells: An Update. Mol. Oncol. 2021;15:1647–1666. doi: 10.1002/1878-0261.12869
9. Song T., Xu A., Zhang Z., Gao F., Zhao L., Chen X., Gao J., Kong X. CircRNA Hsa_circRNA_101996 Increases Cervical Cancer Proliferation and Invasion through Activating TPX2 Expression by Restraining MiR-8075. J. Cell. Physiol. 2019;234:14296–14305. doi: 10.1002/jcp.28128.

HPV VACCINATION - CURRENT CONCEPTS

Dr. Vrinda Joshi
Professor
Department of Obstetrics and Gynaecology
GRMC Gwalior

HPV is the most common viral infection of the reproductive tract and causes a range of conditions in men and women, including precancerous lesions that may progress to cancer.

HPV16 and HPV18 together are responsible globally for 71% of cases of cervical cancer. HPV45 accounts for 6%, HPV31 for 4%, HPV33 for 4%,HPV52 for 3% and HPV58 for 2% of cervical cancer cases. Together, these 7 HPV types account for approximately 90% of the squamous-cell carcinomas that are positive for HPV DNA.

HPV infection with high-risk HPV types is also the cause of a proportion of cancers of the anus, vulva and vagina, penis, head and neck, especially the oropharynx.

HPV infections are restricted to the epithelial layer of the mucosa and do not induce a vigorous immune response. The median time from HPV infection to seroconversion is approximately 8–12 months, although immunological response varies by individual, HPV type and duration of infection. After natural infection, 70–80% of women seroconvert; their antibody responses are typically slow to develop and of low titre and avidity. In men there is less response to natural HPV infection; few men seroconvert and any antibodies produced may not be protective.

Vaccine:

The first vaccine for the prevention of HPV-related disease was licensed in 2006. Currently 6 prophylactic HPV vaccines are licensed. All are intended to be administered, if possible, before the onset of sexual activity, i.e. before exposure to HPV. All vaccines are prepared, using recombinant DNA and cell-culture technology, from the purified L1 structural protein, which self-assembles to form HPV type-specific empty shells, termed virus-like particles (VLPs). HPV vaccines do not contain live biological products or viral DNA and are therefore non-infectious. All HPV vaccines contain VLPs against high-risk HPV.

Types 16 and 18; the nonavalent vaccine also contains VLPs against high-risk HPV types 31, 33, 45, 52 and 58; and the quadrivalent and nonavalent vaccines contain VLPs to protect against anogenital warts causally related to HPV types 6 and 11. All HPV vaccines are indicated for use in females aged 9 years or older, and are licensed for use up to 26 or 45 years of age.

Some HPV vaccines are also licensed for use in males. All HPV vaccines are indicated for the prevention of cervical premalignant lesions and cancers caused by high-risk HPV types,

which vary by vaccine product. As per their product labels,46 selected vaccines have indications against other HPV-related disease. HPV vaccines are available as a prefilled syringe or in single or 2-dose vials. To date, 125 countries (64%) have introduced HPV vaccine in their national immunization programme for girls, and 47 countries (24%) also for boys.

Administration, manufacturers' schedules and storage

The vaccines should be administered intramuscularly in the deltoid region. The standard dose is

0.5 ml. The vaccination schedule, as stipulated by the manufacturers, mostly depends on the age of the recipient. Listed below is information based on the product labels.

Bivalent HPV vaccines:

Cervarix is licensed for girls and boys aged 9–14 years as a 2-dose schedule (5–13 months apart). If the recipient's age at the time of the first dose is ≥15 years, three doses should be given (at 0, 1–2.5 months and 5–12 months).

Cecolin is licensed for girls aged 9–14 years as a 2-dose schedule (6 months apart). From age 15, a 3-dose schedule is indicated (at 0, 1–2 months and 5–8 months).

Walrinvax is licensed for girls aged 9–14 years as a 2-dose schedule (6 months apart, with a minimum interval of 5 months). From age 15, a 3-dose schedule is indicated (at 0, 2–3 and 6–7 months).

Quadrivalent HPV vaccines:

Gardasil is licensed for girls and boys aged 9–13 years as a 2-dose schedule (6 months apart). From age 14, a 3-dose schedule should be given (at 0, 1–2 and 4–6 months).

Cervavax is licensed for girls and boys aged 9–14 years, as a 2-dose schedule (6 months apart). From age 15, a 3-dose schedule should be given (at 0, 2 and 6 months).

Nonavalent HPV vaccine:

Gardasil9 is licensed for girls and boys aged 9–14 years as a 2-dose schedule (5–13 months apart). From age 15,a 3-dose schedule should be followed (at 0, 1–2 and 4-6 months).

Storage of HPV vaccines

All HPV vaccines should be maintained at 2–8 °C. Cervarix is stable and can be stored outside the refrigerator for up to 3 days at temperatures between 8 °C and 25 °C, or for up to 1 day at temperatures between 25 °C and 37 °C. Gardasil and Gardasil-9 are licensed to be stored for 3 days at temperatures from 8 °C to 42 °C (controlled temperature chain (CTC)) or for 4 days at temperatures from 8 °C to 40 °C.

Vaccine immunogenicity, efficacy and effectiveness

HPV vaccines are highly immunogenic. The existing vaccines initiate a strong humoral response with robust memory. In clinical trials, a peak serum antibody titre was observed 4 weeks after the last dose; titres then declined over the subsequent 12–18 months before stabilizing. The serological response to vaccination is much stronger (1–4 logs higher) than the response after natural infection.

The avidity of the polyclonal antibody response is much higher after vaccination than after infection but does not increase appreciably after boosting. The high efficacy of HPV vaccine seen in the clinical trials to date has precluded identification of a minimum protective antibody titre, and there is no known serological correlate of immunity.

Particulate antigens, such as VLPs, can persist for years in lymph nodes and may be the mechanism for the observed avidities after single-dose HPV vaccination.

Duration of protection

With a multidose schedule, antibody titres remain high for at least 12 years for the bivalent (Cervarix) vaccine and quadrivalent (Gardasil) vaccine and for at least 6 years for the more recently licensed nonavalent vaccine.

Vaccination schedule

Two-dose schedule: The current evidence supports the recommendation that a 2-dose schedule be used in the primary target group from 9 years of age and for all older age groups for which HPV vaccines are licensed. The minimum interval between first and second dose is 6 months. A 12-month schedule results in higher GMTs137 and is suggested for programmatic and efficiency reasons. There is no maximum recommended interval between doses and longer intervals-**up to 3 or 5 years – can be considered if useful from a programme perspective.**

Alternative single-dose schedule: As an off-label option, a single-dose schedule can be used in girls and boys aged 9–20 years.

Current evidence suggests that a single dose has comparable efficacy and duration of protection as a 2-dose schedule and may offer programme advantages, be more efficient and affordable, and contribute to improved coverage. From a public health perspective, the use of a single dose schedule can offer substantial benefits that outweigh the potential risk of a lower level of protection if efficacy wanes over time, although there is no current evidence of this.

Schedule for Immuno compromised persons.

Individuals known to be immuno compromised or HIV-infected (regardless of age or antiretroviral therapy status) should receive at least two HPV vaccine doses (minimum 6 months interval) and, where possible, three doses. **Choice of HPV vaccine**

Current evidence suggests that, from a public health perspective, all currently licensed bivalent, quadrivalent and nonavalent vaccines offer comparable immunogenicity,

efficacy and effectiveness for the prevention of cervical precancer and cancer, which is mainly caused by HPV types 16 and 18.

Reference: WHO progress report 2022

RECENT ADVANCES IN OVARIAN CANCER

Dr. Ajay Halder
Associate Professor
Dept. of Obstetrics & Gynaecology
AIIMS Bhopal

INTRODUCTION

Ovarian cancer is the 7th most common cancer in women in the world and 8th most common cause of death from cancer in women in the world. Around 313,959 women are diagnosed every year with 207,252 women die of the disease every year around the world [1]. The risk is even higher in women with familial and known genetic predisposition to this disease[2].

ETIOLOGY

The established risk factors are age and having a family history of the disease. Affected family members constitute a significant risk factor. First degree relatives of proband have a three-seven fold increased risk, often with an early age of onset. The lifetime risk of EOC associated with germline BRCA1 mutation exceeds 50% and that associated with germline BRCA2 mutation ranges from 12-20%. Whereas protective factors include increasing parity, oral contraceptive use and salpingo-oophorectomy. Whereas Lactation, incomplete pregnancies, hysterectomy, tubal ligation may confer a weak protective effect[3].

SCREENING AND PREVENTION

Measurement of CA-125 levels is usually done in adjunction with the imaging. CA-125 is elevated in most of the epithelial ovarian cancers overall, but only half of the early stage epithelial ovarian cancers [9]. The specificity and positive predictive value found to be higher in postmenopausal women. Increased CA-125 levels are also observed in other conditions such as endometriosis, pregnancy, ovarian cysts, inflammatory peritoneal diseases. Hence, other biomarkers are currently being studied to improve specificity for ovarian cancer biomarkers. Human epididymis protein 4 (HE4) is a new biomarker that is currently being evaluated. It is found to be more sensitive for ovarian cancer and found in approximately 100% of serous and endometrioid subtypes. Based on recent studies, a combination of higher CA-125 and HE4 levels are thought to be predictive of malignant ovarian tumours and may serve as a useful diagnostic tool in the future [10]. CA-125 levels can also be used to calculate the risk of malignancy index (RMI), which also utilizes TVUS findings and menopausal status. RMI above 200 is associated with a high risk of malignancy, with a greater than 96 % specificity [8].

The malignancy algorithm (ROMA) risk utilizes a mathematical formula that incorporates HE-4 and CA 125 levels adjusted for pre and post-menopausal status to determine the risk of malignancy [11]. The ROMA is a valuable screening test that takes advantage of the high specificity of HE4 and high-sensitivity of CA-125 to detect more patients of ovarian cancer overall, especially in the early stages.

Use of OCP has been associated with a significant reduction in the risk of ovarian cancer.

CLINICAL FEATURES:

Epithelial ovarian cancer classically presents with vague persistent gastrointestinal, urologic, or nonacute abdominal/pelvic symptoms, shortness of breath, weight loss, early satiety (bloating, early satiety, discomfort, constipation, vaginal bleeding, indigestion and acid reflux). Ultimately, a pelvic examination or imaging identifies an adnexal mass. While germ cell tumour presents at early age of life.

STAGING OF OVARIAN CARCINOMA

Ovarian cancer is staged according to the 8th edition American Joint Committee of Cancer (AJCC), International Federation of Gynecology and Obstetrics (FIGO) staging system and corresponding Tumor, Node, Metastasis (TNM) classification.

Stage I - Tumor limited to ovaries (one or both) or fallopian tube(s)

- IA - Tumor limited to one ovary (capsule intact) or fallopian tube, no tumor on ovarian or fallopian tube surface; no malignant cells in 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 ascites or peritoneal washings

- IC - Tumor limited to one or both ovaries or fallopian tubes, with any of the following:
- IC1 Surgical spill
- IC2 Capsule rupture before surgery or tumor on the ovarian or fallopian tube surface
- IC3 Malignant cells in ascites or peritoneal washings

Stage II - Tumor involves one or both ovaries or fallopian tubes with a pelvic extension below pelvic brim or primary peritoneal cancer

- IIA - Extension and/or implants on the uterus and/or fallopian tube(s) and/or ovaries .
- IIB - Extension to and/or implants on other pelvic tissues .

Stage III - Tumor involves one or both ovaries or fallopian tubes, or primary peritoneal cancer, with microscopically confirmed peritoneal metastasis outside the pelvis and/or metastasis to the retroperitoneal (pelvic and/or para-aortic) lymph nodes.

- IIIA1 - Positive retroperitoneal lymph nodes only (histologically confirmed) .
- IIIA1i - Metastasis up to and including 10 mm in greatest dimension.
- IIIA1ii - Metastasis more than 10 mm in greatest dimension.
- IIIA2 Microscopic extra pelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes.
- IIIB - Macroscopic peritoneal metastasis beyond pelvis 2 cm or less 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 an extension of tumor to the capsule of liver and spleen without parenchymal involvement of either organ).

Stage IV - Distant metastasis, including pleural effusion with positive cytology; liver or splenic parenchymal metastasis; metastasis to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside the abdominal cavity), and transmural involvement of intestine.

- IVA - Pleural effusion with positive cytology.
- IVB - Liver or splenic parenchymal metastases; metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside the abdominal cavity); transmural involvement of intestine.

TREATMENT/MANAGEMENT:

SURGERY:

Surgery is the mainstay of treatment in the cases of carcinoma ovary with a goal of complete resection while the term optimal cytoreduction refers to ≤1 to 2 cm of tumour volume. In the early stages of carcinoma, unilateral salpingo-oophorectomy will be preferred. However, for advanced-stage ovarian cancer, a debulking surgery comprising hysterectomy/bilateral salpingo-oophorectomy (BSO) has shown better outcomes [4]. One of the most powerful independent determinants of improved median survival among patients with stage III or IV ovarian carcinoma is to achieve maximal cytoreduction. Surgical procedures that may be performed in women with ovarian cancer are as follows:

- Surgical staging
- Cytoreductive surgery
- Interval debulking
- Laparoscopic surgery
- Secondary surgery

CHEMOTHERAPY

The use of platinum and taxane based chemotherapy is the gold standard for adjuvant treatment of advanced EOC. Although these drugs are used for all advanced stage EOCs, they are probably most active in high grade serous and undifferentiated carcinoma. Currently, paclitaxel and carboplatin are administered every 3 weeks as the standard agents for the first-line treatment of advanced ovarian cancer. Postoperative chemotherapy is indicated in all patients with ovarian cancer, except those who have surgical-pathologic stage I disease with low-risk characteristics. Standard postoperative chemotherapy for ovarian cancer is combination therapy with a platinum compound and a taxane (eg, carboplatin and paclitaxel). Additional agents for recurrent disease include the following- liposomal doxorubicin, etopside, topotecan, gemcitabine, vinorelbine, ifosfamide, flurouracil, melphalan, alteramine, bevacizumab, Olaparib, niraparib, rucaparib and pazopanib.

The concept of "dose-dense therapy" is based on the Norton-Simon hypothesis that a shorter interval between the doses of cytotoxic agents is more effective in reducing tumour burden than dose escalation.

In cases of recurrent ovarian tumour, Platinum free interval [PFI] refers to the interval between the completion of the last platinum-based chemotherapy and the occurrence of relapse [6]. However, platinum sensitivity is generally used to refer

to an interval of greater than 6 months between the last platinum-based chemotherapy (PBC) cycle and commencement of subsequent PBC. In such cases we can restart with PBC. The European organization for research and treatment of cancer (EORTC), phase III trial EORTC 55971 recruited women with stage IIIC-IV epithelial ovarian cancer (n=670) and CHORUS trial had a similar recruitment profile with women of stage III A-B besides (n= 550). They showed non-inferiority of median overall survival with neoadjuvant chemotherapy when compared to primary cytoreductive surgery upfront [5].

INTRAPERITONEAL CHEMOTHERAPY

Post operative intra peritoneal chemotherapy [IP] and intravenous [IV] combination therapy for advanced ovarian carcinoma has been studied in four phases III trails by the GOG. Regional therapy takes advantage of both the prolonged confinement with the disease within the peritoneal cavity and the steep dose response relationship observed for most cytotoxic agents. In addition, by exploiting the peritoneal -plasma barrier, the rate of drug clearance is slowed from the peritoneal to systemic compartment and creates a concentration differential favouring the peritoneal cavity.

In hyperthermic intraperitoneal chemotherapy [HIPEC] combines the pharmacokinetic advantage inherent to the intracavitary delivery of certain cytotoxic drugs with the direct cytotoxic effect of hyperthermia. Hyperthermia enhances the tissue penetration of the administered drugs. HIPEC can be administerd by open coliseum technique or by a closed technique. Hyperthermic temperature is monitored using temperature probes placed in bladder, oesophagus and inflow and outflow intra-peritoneal[IP] catheters.

OVARIAN CANCER TARGETED THERAPY

ANTI ANGIOGENESIS THERAPY

Bevacizumab (Avastin) belongs to a class of drugs called angiogenesis inhibitors. This drug attaches to a protein called VEGF (that signals new blood vessels to form) and slows or stops cancer growth. The most common side effects are hypertension[≥grade 2], gastro-instestinal fistula, perforation. Importantly, gastro-instestinal wall distrubtion [bleeding and impaired wound healing] are black box warnings.

Bevacizumab can also be given with olaparib as maintainence treatment in women whose cancers have a BRCA gene mutation or genomic instability This drug is given as an infusion into the vein (IV) every 2 to 3 weeks.

PARP INHIBITORS

Olaparib (Lynparza), rucaparib (Rubraca), and niraparib (Zejula) are drugs known as a PARP inhibitors [poly {ADP}-ribose polymerase]. PARP enzymes normally help repair damaged DNA inside cells. Mutations in BRCA genes can make it difficult for a cell to repair its DNA. PARP inhibitors can make it even harder for tumour cells with an abnormal BRCA gene to repair damaged DNA, which often leads to the death of these cells. The most common side effect of niraparib, Olaparib and rucaparib are thrombocytopenia[34%], anaemia[18%] and nausea[25%] respectively.

RADIATION ONCOLOGY

Due to the increased frequency of toxicity and complications, it became non- existent.

REFERENCES

1. GLOBOCON 2020
2. Salehi F, Dunfield L, Phillips KP, Krewski D, Vanderhyden BC. Risk factors for ovarian cancer: an overview with emphasis on hormonal factors. J Toxicol Environ Health B Crit Rev. 2008 Mar;11(3-4):301-21. doi: 10.1080/10937400701876095. PMID: 18368558.
3. Holschneider CH, Berek JS. Ovarian cancer: epidemiology, biology, and prognostic factors. Semin Surg Oncol. 2000 Jul-Aug;19(1):3-10. doi: 10.1002/1098-2388(200007/08)19:1<3::aid-ssu2>3.0.co;2-s. PMID: 10883018.
4. Stewart C, Ralyea C, Lockwood S. Ovarian Cancer: An Integrated Review. Semin Oncol Nurs. 2019 Apr;35(2):151-156.
5. Vergote I, Coens C, Nankivell M, Kristensen GB, Parmar MKB, Ehlen T, Jayson GC, Johnson N, Swart AM, Verheijen R, McCluggage WG, Perren T, Panici PB, Kenter G, Casado A, Mendiola C, Stuart G, Reed NS, Kehoe S., EORTC. MRC CHORUS study investigators. Neoadjuvant chemotherapy versus debulking surgery in advanced tubo-ovarian cancers: pooled analysis of individual patient data from the EORTC 55971 and CHORUS trials. Lancet Oncol. 2018 Dec;19(12):1680-1687.
6. Luvero D, Milani A, Ledermann JA. Treatment options in recurrent ovarian cancer: latest evidence and clinical potential. Ther Adv Med Oncol. 2014 Sep;6(5):229-39. [.
7. Hogen L, Thomas G, Bernardini M, Bassiouny D, Brar H, Gien LT, Rosen B, Le L, Vicus D. The effect of adjuvant radiation on survival in early stage clear cell ovarian carcinoma. Gynecol Oncol. 2016 Nov;143(2):258-263.
8. Smith CG. A Resident's Perspective of Ovarian Cancer. Diagnostics (Basel). 2017 Apr 27;7(2)
9. Cannistra SA. Cancer of the ovary. N Engl J Med. 2004 Dec 09;351(24):2519-29.
10. Dochez V, Caillon H, Vaucel E, Dimet J, Winer N, Ducarme G. Biomarkers and algorithms for diagnosis of ovarian cancer: CA125, HE4, RMI and ROMA, a review. J Ovarian Res. 2019 Mar 27;12(1):28.
11. Moore RG, McMeekin DS, Brown AK, DiSilvestro P, Miller MC, Allard WJ, Gajewski W, Kurman R, Bast RC, Skates SJ. A novel multiple marker bioassay utilizing HE4 and CA125 for the prediction of ovarian cancer in patients with a pelvic mass. Gynecol Oncol. 2009 Jan;112(1):40-6.

ROLE OF LAPAROSCOPY IN GYNAECOLOGICAL MALIGNANCY

Dr. Manesha Shrivastav
Laparoscopic Surgeon and Gynecologist
Bhopal

Laparoscopic approach in malignancies has been explored as early as 1992 as a tool for taking biopsies and replacing second look laparotomies as second look laparoscopies in ovarian cancers. Laparoscopy as surgical approach in treatment of cancers started with the advent of HD camera systems, advanced electrosurgical units and ultrasonic shearers little later.

Laparoscopic approach has certain distinct advantages and disadvantages in cancer surgeries.

The specific advantages are as follows:

1. The magnification resolution and pneumoperitoneum provide better dissection, clearance minimal blood loss.
2. 3D laparoscopic approach gives effortless access to pelvis specially in obese women which is challenging and struggle in conventional approach.
3. Laparoscopic approach can be used to assess operability &to do the sentinel lymph node biopsies avoiding a laparotomy.

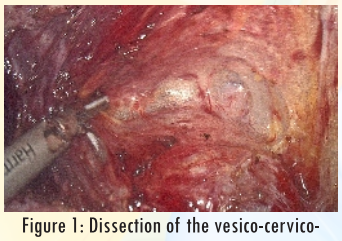


Figure 1: Dissection of the vesico-cervico-vaginal space upto bladder neck

The disadvantages are as follows:

1. Long learning curve to perform these procedures.
2. The challenge in tissue retrieval in case of solid organ malignancies.
3. Tumor/ cyst rupture specially in ovarian cancers.
4. A theoretical risk of allowing malignant cell proliferation due to CO2 pneumoperitoneum was considered as a disadvantage, however studies have disproven it.

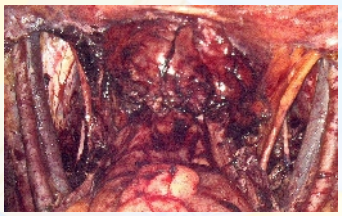


Figure 2: Final view of TLRH

We shall further analyze applications of laparoscopy in various gynecological cancers.

CANCER CERVIX:

In last two decades, laparoscopic approach was increasingly used in radical hysterectomies until LACC (Laparoscopic Approach to Cervical Cancer) trial in 2018 showed a poor disease-free interval and reduced survival in laparoscopic approach as compared to open approach. This led to a significant decrease in number of laparoscopic hysterectomies being performed. The LACC trial had several limitations but it certainly led to a decline in laparoscopic radical hysterectomies.

However in present day there is a definite role of laparoscopy in cervical cancers with growing positive evidence in terms of survival and disease free interval.

Let us now assess the laparoscopic approach in terms of technical feasibility and oncological outcome.

Total Laparoscopic Radical hysterectomy (TLRH) is a technically feasible approach as 3D laparoscopy allows superior visibility and efficient dissection of the pelvic spaces. In fact the operative time & blood loss is much less than open approach. TLRH is performed in Stage 1A1 -Stage 2A.The technique described is laparoscopic adaptation of the Okabayashi's modification (Pune Technique) and since we operate stage1 disease only, we practice the nerve sparing technique in all cases.Following are the standard steps to perform TLRH.

1. A deep cervical conization is always performed 48 hours prior to the TLRH (ref SUCCOR study). This has been

shown to prevent relapses may be dure to tumor dissemination in recent times. However, as a good practice point it has been included in the procedure until more evidence evolves.

2. Patient is positioned Lloyd Davis position & one 10 mm camera port with 3 5mm accessory ports are used. TLRH is always performed in 3D Laparoscopic system
3. "No touch technique" that is no form of uterine manipulation is used, neither vaginal manipulator nor a myoma spiral. This is done to prevent any form of tumor dissemination. Uterus is handled with an atraumatic grasper during the surgery.
4. Posterior U shape incision at the level of pelvic brim is taken starting from the medial aspect of infundubulopelvic ligament from one side to other. The lower limit is deepest part of POD.
5. Dissection of the Rectovaginal space, at least 3-4 cm past the cervix
6. Dissection of the Pararectal space is the most important step which determines the oncological clearance.
7. Dissection of the vesico-cervico-vaginal space anteriorly carried out with an incision extending from the lateral most part of one round ligament to the other. In the midline the peritoneal incision is at the inferior most part of vesical peritoneal fold. The dissection is carried inferiorly right up the bladder neck in order to ensure as adequate vaginal cuff (Figure 1)
8. Individual ligation is done to ensure the adequate parametrial clearance as lateral as possible. Ureter is seen in a "Y" the anterior limb being uterine artery and posterior being uterine vein. Once these are individually ligated or clipped the ureter fall off laterally bringing the whole parametrium in clear vision which is then transected laterally.
9. Dissection of Yabuki's space: It is small retroperitoneal space under the cervico-vesical fold of peritoneum. Ureter traverses this space anteriorly just before entering in the urinary bladder with two conspicuous veins cervico-vesical ligament. These veins may be clipped or ligated. Dissection of this space enables adequate clearance of paracolpos.
10. Ilio-obturator lymphadenectomy is performed the lower limit being obturator nerve, medial limit being internal iliac artery and laterally medial aspect of psoas tendon.
11. We this method a parametrial clearance of up to 3 cm and vaginal cuff of up to 3 cm can be obtained. All the fibrofatty tissue around the iliac vessels is cleared up to the obturator given a nodal harvest of minim15-26 lymph nodes.
12. Nerve sparing method first described by Dr Magara is now widely practiced. The inferior hypogastric plexus lies postero-inferomedial to the ureter and division of the uterine vein just medial to the ureter preserves the nerve. This the cardinal point in nerve preservation.

Hence, we conclude that a TLRH (Figure 1) is technically feasible attainable and safe procedure. However, in long term various RCTs mention poor disease-free survival despite of good oncological clearance. It was also found that the pattern of loco regional recurrence after laparoscopic approach was different from open approach. This led to the concept of no manipulation, no touch method in TLRH and use of pre operative conization to prevent the risk of tumor dissemination improving DFS in laparoscopic approach.

CANCER ENDOMETRIUM: Endometrial cancers are the most common cancer of female genital tract in present day as we are seeing a simultaneous gradual decline is cervical cancers. Laparoscopic approach is well established in surgical management of endometrial cancer and trial have shown laparoscopy to be as efficacious, safe& offering similar DFS as open approach. Most women with endometrial cancer are old, obese, with medical co-morbidities, obesity being one of the risk factors for cancer endometrium. Laparoscopic approach clearly avoids all the added morbidity of laparotomy in these high risk women. Moreover surgery is the mainstay of the treatment in endometrial cancers and therefore aim is to avoid a laparotomy & improve DFS.

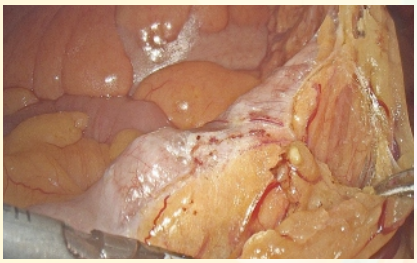
In early-stage low risk disease TLRH with or without pelvic lymphadenectomy is superior to open approach. Pelvic lymphadenectomy has not shown to increase overall survival or DFS in low-risk disease hence it may or may not be done. However, if at all patients with low-risk disease come with recurrence it is loco regional vault/vaginal recurrence. Hence even in low-risk disease good 3 cm vaginal cuff is removed and all precautions of avoiding uterine manipulation is taken to avoid any tumor cell dissemination.

In advanced endometrial cancers role of laparoscopic approach has not been studied however a proper Staging laparoscopy has definite role and is a safe alternative to open approach wherein a TLRH is performed along with pelvic and para-aortic lymphadenectomy along with infracolic omentectomy. However,the comparison of laparoscopic and open approach has been done in advanced or high-risk diseases. Sporadic studies /series do see laparoscopy feasible in advanced endometrial cancers also.

OVARIAN CANCER:

Laparoscopic approach has been used for long in ovarian cancer as a diagnostic tool. Established indications of laparoscopy in ovarian cancers are as follows:

1. Staging laparoscopy in early ovarian cancer
2. Laparoscopic assessment of disease extent and resectability/ operability
3. Laparoscopic second-look operation to rule out recurrence.



Infracolicomentectomy performed in Staging laparoscopy

Limitation of laparoscopy in ovarian cancer

1. Tumour dissemination due to cyst rupture and incomplete staging.
2. Port site metastasis
3. Challenges of specimen retrieval

Step by Step Staging Laparoscopy for ovarian cancers:

1. Peritoneal washings from pelvis and sub diaphragmatic region
2. Random peritoneal biopsies from pelvic peritoneum overlying the uterosacral ligament
3. Hysterectomy
4. Bilateral adnexectomy
5. Infracolic omentectomy
6. Appendectomy
7. Pelvic and paraaortic lymphadenectomy

In case of large tumors, tissue retrieval becomes a challenge and upstaging of disease occurs while retrieval due to spillage. However, does upstaging of disease due to surgical spillage cause poor prognosis or not is still not studied & debatable. Enbag vaginal retrieval or use of morsafe endobags prevent lost pieces or solid tissue spillage. They do not prevent tumor dissemination. Hence large solid tumors always are a challenge in laparoscopic approach.

PELVIC & PARA-AORTIC LYMPHADENECTOMY

Lymphadenectomy remains the mainstay of any surgical treatment performed for malignancy. Studies have shown with good quality evidence that laparoscopic approach is comparable to open approach as far as nodal harvest is concerned with lesser blood loss, lesser operative time and lesser complications. However, to perform it by laparoscopic approach surgeon should be trained well with thorough knowledge of anatomy. In cervical cancers a complete clearance of ilioobturator chain is desirable. In endometrial cancers when there is cervical invasion, myometrial invasion greater than half, poorly differentiated histology, tumor size of more than 4 cm or positive pelvic lymph nodes, a complete para-aortic lymphadenectomy is desired and clearance has positive effect on survival for high-risk disease.

Anatomical Landmarks for pelvic lymphadenectomy:

1. Lateral boundary: Genitofemoral nerve
2. Medial boundary: Internal iliac artery or Obliterated hypogastric artery
3. Caudal boundary: Up to Deep circumflex vein
4. Inferior boundary: Obturator nerve

Anatomical Landmarks for paraaortic lymphadenectomy:

1. Lateral boundary: Ureters on both sides
2. Superiorly: B/L Renal veins & Ovarian artery

3. Inferiorly: Common Iliac artery

The ports are placed higher (Le Huang point for camera) in case of paraaortic lymphadenectomy. Laparoscopic approach has allowed good clearance with lesser blood loss owing to excellent vision and resolution.

Good optics, planed port placement, and use of T lifts for retroperitoneal exposure makes pelvic and paraaortic lymphadenectomy attainable in hands of experienced laparoscopic surgeons.

Figure 4: Obturator nerve transection being repaired laparoscopically during pelvic lymphadenectomy.

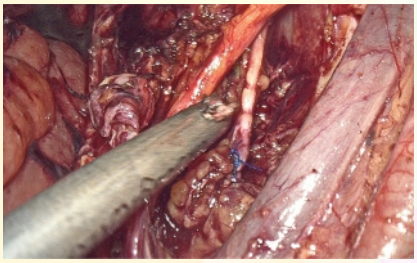


Figure 4: Obturator nerve transection being repaired laparoscopically during pelvic lymphadenectomy.

SENTINEL LYMPHNODE BIOPSY AND USE OF INDIGOCYANINE GREEN

Lymphadenectomy has an important role in surgical staging of gynaecological cancers however many recent studies suggest that lymphadenectomy itself does not increase an overall survival among patients. In fact, the morbidities of procedure are significant in terms of blood loss, nerve injury, lymphocyst formation and are added without any survival benefit. In last few years sentinel lymph node biopsy has emerged at technique to treat patient appropriately with minimal intervention at the same time without any compromise in oncological outcome.

Technique of Sentinel lymph node(SLN)biopsy: SLN mapping is done by injecting the ICG dye into cervical stroma at 3 o'clock and 9o'clock position and submucosally. The recommended concentration of 0.5mg/ml and 1 ml each is injected at each site.

SLNs are visualized using ICG camera platform as green colour lesions which are harvested individually and sent for histopathological examination. The technique is better performed by laparoscopic method than by open method.

Laparoscopy in oncology has a long learning curve. Only Surgeons with adequate experience in the field should perform oncological procedures. A thorough knowledge of anatomy is inevitable. 3D camera operating systems, Indigo cyanine green dye and the ICG camera allows tailor made surgical treatment by laparoscopy without compromising the oncological outcome.

KEY POINTS:

1. *In early stage cervical cancers TLRH is an effective alternative to open radical hysterectomy with comparable results.*
2. *The pattern of recurrence after laparoscopy is different from open method surgery and it was concluded that this could be because of tumour dissemination.*
3. *A no touch technique to the tumour is to be always used and no uterine manipulator is used, neither vaginal nor myoma spiral to prevent any tumour dissemination.*
4. *A pre operative conisation is supposed to decrease the risk of tumour dissemination and is good practice to perform minimum 48 hours prior to TLRH.*
5. *Laparoscopic approach is established in management of cancer endometrium with good DFS.*
6. *It is important to remove a good vaginal cuff of about 2 cm as it prevents any locoregional/vault recurrence even in low risk diseases.*
7. *Staging laparoscopy in early stage ovarian cancer is safely performed by laparoscopic approach and is the route of choice.*
8. *Laparoscopic cytoreduction in advanced or interval ovarian cancers is not recommended due to limitation in tissue retrieval, tumour dissemination and port site metastasis.*
9. *Laparoscopic approach is highly efficient way to perform pelvic and paraaortic lymphadenectomy giving comparable nodal yield with lesser blood loss.*
10. *Sentinel lymph node biopsy and use of ICG dye is best done by laparoscopic approach.*

POST MENOPAUSAL BLEEDING -A COMPREHENSIVE EVALUATION

Dr Sonal Sahni
Associate Professor
Department of Obstetrics & Gynaecology
N.S.C.B. MCH Jabalpur (M.P.)

Dr. Kirti Patel
Assistant Professor
Department of Obstetrics & Gynaecology
N.S.C.B. MCH Jabalpur (M.P.)

Pay attention to bleeding in menopause;
It can save a life ....

Introduction

Postmenopausal bleeding is a common complaint with a broad differential, which includes both benign and malignant conditions. It is defined as an episode of bleeding occurring 12 months or more after the final menstrual period[1]; however it is recommended that any vaginal bleeding that occurs 6 months after the last period (presumed menopause) should be investigated. Post menopausal bleeding is reported in about 4-11% of women[2] and it accounts for approximately 5% of gynecologic office visits[3] postmenopausal bleeding is "endometrial cancer" until proven otherwise, although only 1-14% of such patients will actually have endometrial cancer. Vaginal bleeding is the presenting sign in more than 90% of postmenopausal women with endometrial cancer[4].

Etiopathology

Postmenopausal bleeding usually attributed to an intrauterine source ,but it may arise from the cervix, vagina ,vulva and ovaries. The origin of bleeding can also involve non-gynaecologic sites, such as the urethra, bladder, anus/rectum/bowel, or perineum.Possible causes of postmenopausal include endometrial atrophy (most common),endometrial polyps,hyperplasia,estrogen therapy ,cancers(Table -1). Lack of estrogen causes atrophy of the vagina and endometrium. Inside the uterus, the collapsed and atrophic surfaces of the endometrium contain scanty or no fluid to prevent friction inside the cavity [5] This leads to the development of micro-erosions of the epithelial surface, with subsequent chronic inflammation. This chronic endometritis is prone to spotting or light bleeding. On the other hand, premalignant or malignant conditions of the endometrium often arise after unopposed estrogen. Systemic estrogen-only therapy, chronic anovulation (such as in polycystic ovarian syndrome), obesity, and estrogen-secreting tumors can lead to abnormal endometrial changes. Anovulation also leads to infrequent, insufficient shedding of the endometrium. Some women have genetic predispositions to endometrial cancer, including Lynch syndrome and Cowden disease[6].

Table 1 Causes of Postmenopausal bleeding

S.NO.	CAUSES
1	ATROPHY-ENDOMETRIAL OR VAGINAL
2	ENDOMETRIAL HYPERPLASIA WITH OR WITHOUT ATYPIA
3	ENDOMETRIAL OR CERVICAL POLYPS
4	ENDOMETRIAL CANCER
5	INFECTION-ENDOMETRIAL, CERVICAL OR VAGINAL
6	DRUGS-POST- MENOPAUSAL HORMONE THERAPY, TAMOXIFEN , ANTICOAGULANTS, HERBAL SUPPLEMENTS(PHYTOESTROGEN)
7	CERVICAL CANCER, VAGINAL OR VULVAR CANCER, OVARIAN CANCER, ESPECIALLY ESTROGEN-SECRETING TUMOUR
8	FORGOTTEN PESSARY
9	POST-RADIATION EFFECTS
10	NON- GYNAECOLOGICAL SUCH AS TRAUMA OR BLEEDING DISORDER.

Evaluation

History

The nature of current bleeding – first episode, persistent or recurrent, duration, frequency, length and quantity of bleeding and its relation with coitus, pain should be elicited. Previous menstrual history, parity, past medical and family history of breast, colon, and endometrial cancer need to be elicited. Women with family history of hereditary non-polyposis colorectal cancer have a lifetime risk of developing endometrial cancer of around 42-60%.The presence of other co-morbid factors such as Diabetes, Hypertension, and use of unopposed Estrogen therapy, should be recorded. In addition the women should be asked about history of treatment with Herbal supplements (Phytoestrogen), Tamoxifen, Tibolone and cyclical/continuous combined HT. Early menarche and late menopause are also associated with increased likelihood of Endometrial hyperplasia / Carcinoma.

Examination

A thorough general and local examination is mandatory. Focus of this is to rule to determine site of bleeding & to rule out vulval, vaginal, cervical and pelvic pathology. Clinical examination should include Speculum examination, Bimanual examination & digital rectal examination. Findings of atrophy classically include pale dry vaginal epithelium that is shiny smooth and lacking rugae. Signs of inflammation include erythema or redness, petechiae, friability, discharge, visible blood vessels through thin epithelium or bleeding. Haematuria and bleeding per rectum (Haemorrhoids) should be kept in mind. The conventional Pap smear or Liquid Based Cytology can detect abnormal endometrial cells in upto 30% of the cases. Lastly, a general systemic examination is essential to identify signs of chronic or severe illness.

Investigations

The principal aim of investigation is to identify or exclude endometrial pathology, most notably endometrial carcinoma.

TVS

The initial assessment in all cases of PMB should be using the TVS. Measurement of the endometrium on TVS should include the full double thickness of the endometrium with any content within the endometrial cavity. The American College of Obstetricians and Gynecologists recommend transvaginal ultrasound for initial evaluation4. The endometrial thickness is measured in an anterior-posterior fashion, at the area of endometrial echo of maximal thickness, on a long-axis view of the uterus4. If endometrial thickness >4 mm, hysteroscopic evaluation and endometrial sampling is recommended. An endometrial thickness of less than or equal to 4 mm has a negative predictive value greater than 99% for endometrial carcinoma. A thin endometrial echo does not reliably exclude type 2 endometrial cancer (uterine papillary serous, mucinous, clear cell) USG also provides an opportunity to identify leiomyomas, adenomyosis, polyp or pathology of the adnexa. A thickened endometrial echo may be caused, not by hyperplasia or malignancy, but by intracavitary lesions such as endometrial polyps. If ultrasound findings are suggestive of such lesions, or if there is a history-indicated suspicion (for example, prior polyps), additional imaging may help to identify if a polyp or other intracavitary lesion is present. Saline-infusion ultrasonography or hysterosalpingogram may be useful in these cases.

Endometrial Sampling

Indications

1) Findings on ultrasound for which endometrial sampling are indicated include:
   a. A thickened endometrial lining greater than 4 mm
   b. Diffuse or focally increased echogenicity or heterogeneity
   c. The inability to visualize the endometrium adequately
2) Endometrial sampling should also be obtained in patients with persistent or recurrent bleeding, even in thin endometrial echo
3) Asymptomatic postmenopausal women with endometrial thickness>11mm (secondary finding)1

The use of 4 mm endometrial thickness as a threshold may miss endometrial cancer for 1 in 339 patients4. The diagnostic accuracy of endometrial sampling correlates positively with the amount of tissue that is collected7.

Methods of endometrial sampling.

1) Dilation and curettage- has been used for years, now a days isolated d & c should not be used because

approximately 60% of curettage specimens sample less than half of the uterine cavity so there is chance of missing pathology1.

2) Office endometrial biopsy using metal curettes or flexible plastic samplers.
3) Hysteroscopy guided endometrial sampling (Gold standard)

Office endometrial biopsy (metal curette or flexible plastic sampler) is a blind sampling method & it may miss focal lesions or intrauterine pathology. It is common for endometrial sampling to result in findings that are insufficient for diagnosis, with rates of sampling failure up to 54%4.If sampling was performed first and was inadequate; a follow-up ultrasound may be performed. If a subsequent transvaginal ultrasound shows a thin endometrium, and if bleeding has stopped, no further evaluation is necessary. For patients with insufficient sampling, or with persistent vaginal bleeding in whom focal lesions may have been missed, additional evaluation should be considered. Hysteroscopy with dilation and curettage or directed biopsy may be warranted in these patients.

MRI

MRI is of value only in Endometrial carcinoma in delineating the size , site and myometrial invasion. It is considered the most accurate imaging technique for preoperative assessment of endometrial cancer due to its excellent soft tissue contrast resolution .Its accuracy is 98% and 90% for myometrial and cervical stromal invasion respectively.The presence of enlarged lymph nodes and cervical involvement can be made out.

Treatment

Treatment of postmenopausal bleeding is focused on the cause; it depends on findings of diagnostic evaluation. Exclusion of cancer is main objective.

Endometrial Hyperplasia-

Treatment of endometrial hyperplasia mainly depends on histological classification and risk factors (obesity, ovulatory dysfunction, increased age, genetic risk)

New WHO 2014 classification of endometrial hyperplasia

Hyperplasia without atypia.

Hyperplasia with atypia or Endometrial Intraepithelial Neoplasia (EIN).

Endometrial hyperplasia without atypia	Endometrial hyperplasia with atypia/EIN
The risk of progression to invasive malignancy is less than 5 %	The risk of progression to invasive malignancy- as high as 27.5% if not treated. Possibility of coexistent endometrial malignancy in atypia/EIN is in around 43% of cases.
Repeat endometrial biopsy every 3-6 months upto 1 year or until biopsy show normal.	Hysterectomy is curative & preferred treatment
Progestin therapy, LNG-IUS (rate of regression upto 90%)	Progestin therapy (LNG-IUS) shown regression upto 75-85%
Hysterectomy if a) No improvement b) Normal endometrium not achieved c) Atypical hyperplasia or carcinoma develop	Note-Endometrial ablation, morcellation or supracervical hysterectomy should never be performed.

Endometrial Malignancy/Endometrial Adenocarcinoma-

Hysterectomy with comprehensive staging is recommended. Comprehensive staging consists of total hysterectomy, bilateral salpingo-oophorectomy, pelvic para-aortic lymphadenectomy and collective peritoneal washing for cytology. Staging allows for appropriate diagnosis, determination of prognosis, and to triage patients for adjuvant therapy appropriately. FIGO committee updated new staging system. The updated 2023 staging includes the various histological types, tumour pattern, and molecular classification to better reflect the improved understanding of the complex nature of the several types of endometrial carcinoma and their underlying biological behaviour.

Table 2-2023 FIGO Staging of cancer endometrium[8]

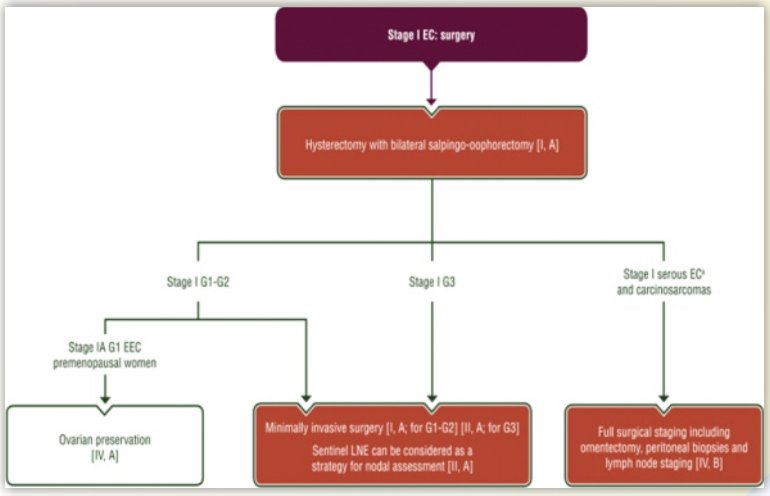
Stage I	Confined to the uterine corpus and ovary
IA	Disease limited to the endometrium OR non-aggressive histological type, i.e. low-grade endometroid, with invasion of less than half of myometrium with no or focal lymphovascular space involvement (LVSI) OR good prognosis disease.
IA1	Non-aggressive histological type limited to an endometrial polyp OR confined to the endometrium.
IA2	Non-aggressive histological types involving less than half of the myometrium with no or focal LVSI.
IA3	Low-grade endometrioid carcinomas limited to the uterus and ovary.
IB	Non-aggressive histological types with invasion of half or more of the myometrium, and with no or focal LVSI.
IC	Aggressive histological types limited to a polyp or confined to the endometrium.
Stage II	Invasion of cervical stroma without extrauterine extension OR with substantial LVSI OR aggressive histological types with myometrial invasion.
IIA	Invasion of the cervical stroma of non-aggressive histological types.
IIB	Substantial LVSI of non-aggressive histological types.
IIC	Aggressive histological types with any myometrial involvement.
Stage III	Local and/or regional spread of the tumor of any histological subtype IIIA Invasion of uterine serosa, adnexa, or both by direct extension or metastasis.
IIIA1	Spread to ovary or fallopian tube (except when meeting stage IA3 criteria).
IIIA2	Involvement of uterine subserosa or spread through the uterine serosa.
IIIB	Metastasis or direct spread to the vagina and/or to the parametria or pelvic peritoneum.
IIIB1	Metastasis or direct spread to the vagina and/or the parametria.
IIIB2	Metastasis to the pelvic peritoneum.
IIIC	Metastasis to the pelvic or para-aortic lymph nodes or both[f].
IIIC1	Metastasis to the pelvic lymph nodes.
IIIC1i	Micrometastasis.
IIIC1ii	Macrometastasis.
IIIC2	Metastasis to para-aortic lymph nodes up to the renal vessels, with or without metastasis to the pelvic lymph nodes.
IIIC2i	Micrometastasis.
IIIC2ii	Macrometastasis.
Stage IV	Spread to the bladder mucosa and/or intestinal mucosa and/or distance metastasis.
IVA	Invasion of the bladder mucosa and/or the intestinal/bowel mucosa.
IVB	Abdominal peritoneal metastasis beyond the pelvis.
IVC	Distant metastasis, including metastasis to any extra- or intra-abdominal lymph nodes above the renal vessels, lungs, liver, brain, or bone.

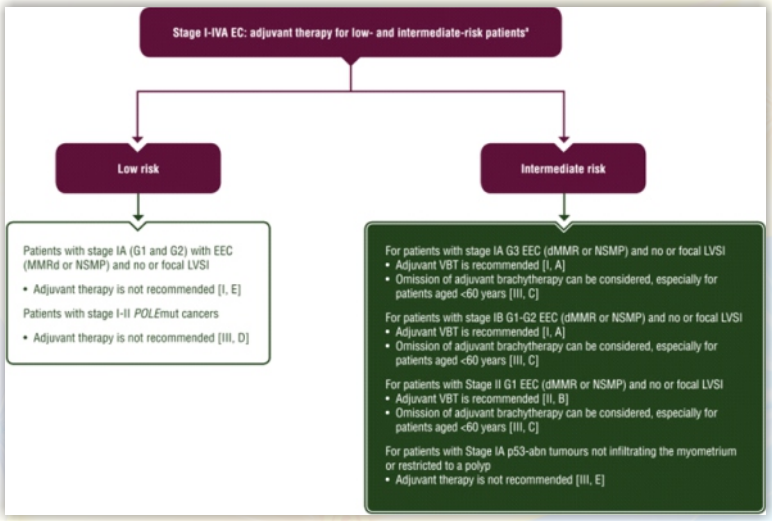
Treatment-

Endometrial cancer is surgically staged and pathologically examined, in all stages, the grade of the lesion, the histological types and LVSI must be recorded. If available and feasible ,molecular classification testing (POLEmut,MMRd,NSMP,p53abn) is encouraged in all patients with endometrial cancer for prognostic risk group stratification9.Treatment of endometrial cancer depends on stage (table 2), histopathological type and grade, and on subgroup of risk classification system(Table 3)

Table 3 Endometrial Cancer risk groups

Risk group	Description
Low risk	Stage IA (G1-G2) with endometroid type (dMMR and NSMP) and no or focal LVSI. Stage I/II POLEmut for stage III POLEmut cancer.
Intermediate risk	Stage IA G3 with endometrioid type (dMMR and NSMP) and no or focal LVSI. Stage IA non-endometrioid type (serous, clear-cell, undifferentiated carcinoma, carcinosarcoma, mixed) and/or p53-abn cancers without myometrial invasion and no or focal LVSI. Stage IB (G1-G2) with endometrioid type (dMMR and NSMP) and or no focal LVSI. Stage II G1 endometrioid type (dMMR and NSMP) and no or focal LVSI.
High-intermediate risk	Stage I endometrioid type (dMMR and NSMP) any grade and any depth of invasion with substantial LVSI. Stage IB G3 with endometrioid type (dMMR and NSMP) regardless of LVSI. Stage II G1 endometrioid type (dMMR and NSMP) with substantial LVSIStage II G2-G3 endometrioid type (dMMR and NSMP).
High risk	All stages and all histologies with p53-abn and myometrial invasion. All stages with serous or undifferentiated carcinoma including carcinosarcoma with myometrial invasion. All stage III and IVA with no residual tumour, regardless of histology and regardless of molecular subtype.



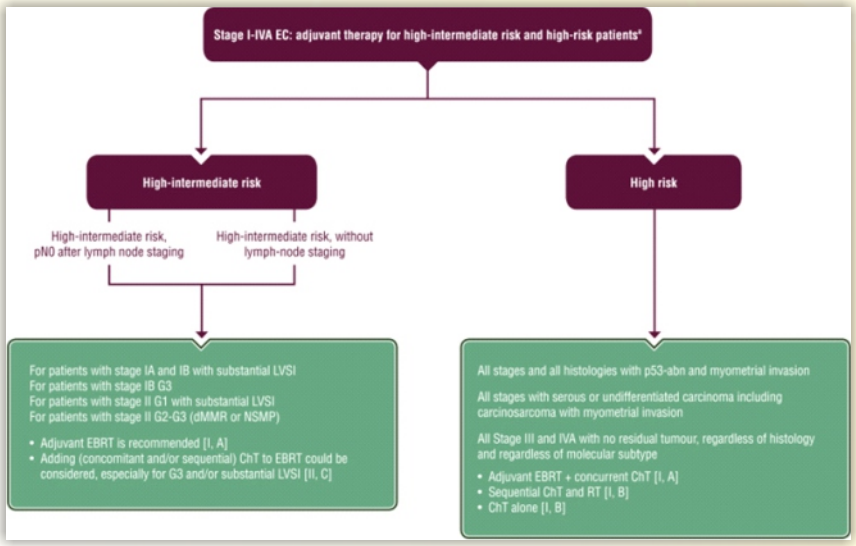


dMMR, mismatch repair deficient; EC, endometrial cancer; G1-G3, grade 1-3; IHC, immunohistochemistry; LVSI, lymphovascular space invasion; MSI-H, microsatellite instability high/hypermutated; NSMP, no specific molecular profile; p53-abn, p53-abnormal; ***POLEmut***, polymerase epsilon-ultramutated.

a Stage III-IVA if completely resected without residual disease; table does not apply to stage III-IVA with residual disease or for stage IV.

b dMMR and MSI-H: Both terms identify a similar EC population. Identification of a defective mismatch repair pathway by IHC (i.e. dMMR) or sequencing to determining microsatellite instability (i.e. MSI-H).

c POLEmut stage III might be considered as low risk. Nevertheless, currently there are no data regarding safety of omitting adjuvant therapy.



Atrophic vaginitis is a common cause of PMB and is effectively treated with local application of estrogen.

Endometrial polyps are best removed during the Hysteroscopic evaluation and sent for HPE. The endometrium should also be sampled and sent for HPE as the likelihood of Endometrial hyperplasia is high (3% of polyps)

Submucous leiomyoma- Hystroscopic removal of leiomyoma, hysterectomy

Endometritis or Cervicitis-Antibiotics should be given.

KEY POINTS

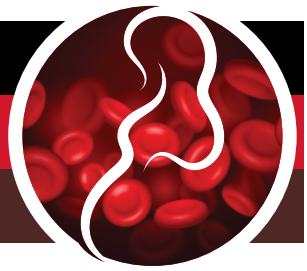
1. Postmenopausal bleeding is "endometrial cancer" until proven otherwise, although only 1-14% of such patients will actually have endometrial cancer.
2. Women with PMB with an endometrial thickness of >4mm should undergo endometrial sampling.
3. Hysteroscopy guided endometrial sampling is considered gold standard as it helps in indentifying other endometrial pathology like endometrial polyp, submucous leiomyoma, intrauterine adhesions or other focal pathology
4. Isolated dilatation and curettage should not be used as the first line method for obtaining endometrial sampling.
5. Women on Tamoxifen with abnormal uterine bleeding should be offered diagnostic hysteroscopy with endometrial sampling as TVS for assessment of endometrium in these women is not useful for triage.
6. Endometrial sampling should also be obtained in patients with persistent or recurrent bleeding, even in thin endometrial echo
7. In patients with endometrial cancer should undergo surgical staging, including hysterectomy ,bilateral salpingo-oophorectomy,peritoneal cytology and sentinel node biopsy or sentinel lymphadenectomy(LNE)
8. In all stages of EC, the grade of the lesion, the histological types and LVSI must be recorded. If available and feasible ,molecular classification testing (POLEmut,MMRd,NSMP,p53abn) is encouraged in all patients with endometrial cancer for prognostic risk group stratification8.

Reference

1. National clinical practice guideline on assessment and management of postmenopausal bleeding dec2022
2. NCBI bookshelf,A service of the National Library of Medicine,National Institute of Health,statpearls ;2023jan
3 Moodley M, Roberts C. Clinical pathway for the evaluation of postmenopausal bleeding with an emphasis on endometrial cancer detection. J Obstet Gynaecol. 2004 Oct;24(7):736-41. [PubMed: 15763777]
4 ACOG Committee Opinion No. 734: The Role of Transvaginal Ultrasonography in Evaluating the Endometrium of Women With Postmenopausal Bleeding. Obstet Gynecol. 2018 May;131(5):e124-e129. [PubMed: 29683909]
5. Annals of oncology ,ESMO,https;//doi.org/10.1016/j.annoc.2022.05.009

INDIA'S 1st Taurine-powered Ferrous Ascorbate TABLET

R. B. TONE® RAPID TABLET



Ferrous Ascorbate 100mg + Taurine 250mg + Folic Acid 1.5mg

RAPID Hb Rise for Optimal Pregnancy Outcome

50% of Bacterial vaginosis patients experience recurrent infection with antibiotic therapy alone[1]

Presenting,

Evebact

L. crispatus 1 Billion CFU, L. rhamnosus 1 Billion CFU, L. gasseri 30 Million CFU, L. jensenii 20 Million CFU, Fructooligosaccharides 100 mg Veg Capsule

Restores Vaginal Flora... Reduces Recurrence

medley