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STANDING TOGETHER FOR ENCOMPASSING AND PROTECTING WOMEN'S HEALTH

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PRESIDENT

DR JIGYASA DENGRA
SECRETARY

DR KAVERI SHAW PATEL
EDITOR IN CHIEF

DR KIRTI PATEL
CO-EDITOR

E-mail : editorkaveri@gmail.com **Website :** www.jabalpurobgynsociety.org

: jabalpur.fogsi

STAGEWISE TREATMENT OF CANCER CERVIX :SIMPLIFIED

Dr Piyush Jain
MBBS, MD (RT),IGRT/RPM(POLAND)
Director Radiation Oncology Hyd.
Omega Hospital, Jabalpur MP.

Globally cervical cancer continues to be one of the most common cancer in women.In India it is the second leading cause of cancer related death in women, with a mortality rate of 9.1 %, as per GLOBOCAN 2020.A good clinical examination and staging workup is of paramount importance in the management of cancer cervix. Once confirmed histopathologically and staging is done, appropriate treatment can result in excellent outcomes not only in early stage but also in locally advanced cancer cervix.

Treatment options Stagewise-

Stage 1 **Tumour confined to cervix**

Stage IA1 (stromal invasion ≤3 mm in depth)

Fertility sparing treatment options-

A **cone biopsy** is the preferred procedure

- Margin negative - Observation
- Margin positive - repeat cone biopsy or a radical trachelectomy.
- Lymphovascular invasion (LVI)+ - treated the same as stage IA2 disease

Non fertility sparing treatment options.

Total hysterectomy (abdominal or vaginal) for LVI negative .Ovaries can be preserved in young women.

Medically Inoperable :Intracavitary radiation alone, One or 2 intraravitary insertions may be considered up to a dose of 10,000 - 12,500 cGy vaginal surface dose.

Stage 1A2/1B1

IA2 (stromal invasion >3 mm to <5 mm in depth)

IB1 (>5 mm depth of stromal invasion and Invasive carcinoma ≤2 cm)

Fertility sparing treatment options for -

Radical trachelectomy + pelvic lymphadenectomy.

Non Fertility sparing treatment options for

1) **Radical hysterectomy (type II) with pelvic node dissection**
2) **Radiation Therapy:** Radical external pelvic irradiation(EBRT)+ intracavitary (ICRT)

Stage 1B2/1B3

1B2 (Invasive carcinoma >2 cm and ≤4 cm)

IB3 (Invasive carcinoma >4 cm)

Fertility sparing treatment options – Not Valid

Other Treatment Options

1) **Radical hysterectomy (typeIII) and bilateral pelvic lymphadenectomy** ± para-aortic lymphadenectomy.

2) Radical Radiation therapy (EBRT) plus chemotherapy + ICRT.

Adjuvant therapy after radical surgery

High risk: (1) Lymph node metastases, (2)+ve surgical margins, (3)parametrial extension.

Adjuvant chemoradiation therapy with external pelvic radiation therapy with concurrent weekly cisplatin chemotherapy is recommended.

Intermediate risk: (1) Deep invasion of cervical stroma, (2)lymphovascular space invasion, (3)tumour size >4 cm.

Adjuvant radiation therapy is recommended if at least two of the above are present.

Low risk : All other patients:

No adjuvant therapy recommended.

Stage 2: cervical carcinoma invades beyond the uterus + UPPER 2/3rd of vagina

Stage IIA(Without parametrial invasion)

Treatment Options:

1) **Radical hysterectomy (typeIII) and bilateral pelvic lymphadenectomy** ± para-aortic lymphadenectomy.
2) Radical Radiation therapy (EBRT) plus chemotherapy + ICRT.

Stage IIB(With parametrial invasion)

Treatment Options

Inoperable: Hence Platinum based concomitant pelvic chemoradiation + ICRT remains the mainstay of treatment.

Stage 3: The carcinoma involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or non-functioning kidney and/or involves pelvic and/or paraaortic lymph nodes.

Treatment Options

Para-aortic LN –ve: Platinum based concomitant PELVIC chemoradiation + ICRT .

Para-aortic LN +ve: Platinum based concomitant EXTENDED chemoradiation + ICRT .

Stage 4: The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum.

Treatment Options

IVA: Spread of the growth to adjacent organs

A short palliative regime of 30Gy in 10 fractions over two weeks is generally used and in few patients who respond very well, this is followed by intracavitary applications.

IVB: Spread to distant organs

Incurable Stage of disease.

Radiation therapy can be used for palliation of central disease or distant metastasis and Palliative Chemotherapy.

POINTS TO REMEMBER

1) Cancer cervix upto stage III and select stage IVA is considered curable.
2) Long term outcome in operable cancer cervix is similar with single modality surgery or radiotherapy(RT). Surgery should only be considered in patients where requirement of adjuvant RT is minimal.
3) If radiological imaging is highly suspicious of pelvic or para aortic nodal mets in operable cancer cervix,it up stages the disease to IIIC1/IIIC2.
4) There is no role of chemotherapy alone in curative treatment of cancer cervix.
5) Radiotherapy of cancer cervix especially in post op cases should be done using high end RT techniques like IMRT,VMAT. This significantly reduces bladder and bowel toxicities.

WEEKLY INDUCTION CHEMOTHERAPY FOLLOWED BY STANDARD CHEMORADIATION IN PATIENTS WITH LOCALLY ADVANCED CERVICAL CANCER : RECENT TREND

Dr Rajesh Kumar Jain
MD Radiation Oncology
Associate Professor
State Cancer Institute
NSCB Medical College Jabalpur.

Locally advanced cervical cancer (LACC) is treated with standard definitive chemoradiation (CRT). However, many patients relapse locally and also die from metastatic disease. A feasibility study demonstrated a good response rate to short course weekly induction chemotherapy delivered before standard CRT.

Globally, cervical cancer is the fourth most common cancer in women, with around 660 000 new cases in 2022. In the same year, about 94% of the 350 000 deaths caused by cervical cancer occurred in low- and middle-income countries.

The highest rates of cervical cancer incidence and mortality are in sub-Saharan Africa (SSA), Central America and South-East Asia.In India, cervical cancer is the first most frequently diagnosed cancer in rural females and second most common cancer in urban females.

Regional differences in the cervical cancer burden are related to inequalities in access to vaccination, screening and treatment services, risk factors including HIV prevalence, and social and economic determinants such as sex, gender biases and poverty.

The primary cause of pre-cancerous and cancerous cervical lesions is infection with a high-risk or oncogenic HPV types. Most cases of cervical cancer occur as a result of infection with HPV16 and 18. High-risk types, especially HPV16, are found to be highly prevalent in human populations. Cervical cancer tend to occur at the squamo-columnar junction which is an area of active proliferation and metaplasia.

Women living with HIV are 6 times more likely to develop cervical cancer compared to the general population, and an estimated 5% of all cervical cancer cases are attributable to HIV.

According to report of National Cancer Registry Programme 2020, 60.0 % of the cancer cervix uteri patients were diagnosed at locally advanced stage whereas only 32.8% cases were diagnosed in early stage.

Despite all latest technology advancement in treatment of advanced cancer, the overall survival (OS) for stage IIB and III–IV cancer is approximately 60–65% and 25–50%, respectively, which are very disappointing. This higher failure rates are may be due to hypoxic focuses inside large volume tumor and presence of micro metastasis.

Early diagnosis and screening programs are still the best strategies to improve the outcomes of the treatment. Major risk factors identified in epidemiologic studies are sex at young age, multiple sexual partner, history of sexually transmitted diseases, poor genital hygiene and smoking.

The standard treatment for locally advanced cervical cancer (LACC) is currently concurrent chemo radiation (CCRT). Therefore, it is imperative to develop new treatment strategies to improve survival.

The aim of chemotherapy preceding local modalities is to reduce the volume of the disease, making subsequent irradiation or surgery more effective while controlling the micrometastatic disease. The response rate, Specifically the clinical and pathological responses to NACT, ranged from 58.49 to 86.54% and 7.5 to 78.81%, prior to chemotherapy(CRT) compare to the rate of 64%.

The treatment response indicated that locally advanced cervical cancer (LACC) was sensitive to chemotherapy. In addition, the Combined analysis showed that a better clinical response and pathologic response to Neoadjuvant chemotherapy NACT were associated with favorable progression free survival PFS and overall survival OS.

Studies have suggested that adding adjuvant Chemotherapy leads to better outcomes than chemoradiation therapy alone especially in paraaortic spread cervical cancer patients, but associated with increased toxicity. So this approach of treatment not accepted in standard treatment. Prognostic factors include clinical stage at the time of diagnosis, tumor size, lympho-vascular invasion, parametrial and lymph node involvement.

The rationale for using the neoadjuvant chemotherapy approach in patients with cervical cancer has been to reduce the size of primary tumor , increase probability of complete resection ,eradication micro metastasis. Currently some studies have been conducted regarding the usefulness of adding chemotherapy before Chemoradiation.

The INTERLACE Trial was presented in presidential symposium at the ESMO CONGRESS 2023 showed a progression-free survival (PFS) rate of 73% and an overall survival (OS) rate of 80% at 5 years with induction chemotherapy prior to chemoradiotherapy (CRT) compared to rates of 64% (hazard ratio [HR] 0.65; 95% confidence interval [CI] 0.46–0.91; p=0.013) and 72% (HR 0.61; 95% CI 0.40–0.91; p=0.04), respectively, with CRT alone in locally advanced cervical cancer.

The combination of taxanes and platins is known to be active in advanced and recurrent cervical cancer with response rates of 40% - 50%. short course of weekly dose dense paclitaxel and carboplatin chemotherapy before chemoradiation (CRT) might downstage local diseases, lengthen the exposure to systemic treatment and improve the outcome.

ADVANCEMENTS IN GYNECOLOGIC ONCOLOGY THROUGH ROBOTIC SURGERY: A MODERN PERSPECTIVE

Dr. Jagadishwar Goud Gajagowni
MBBS, MS (Gen. Surgery), MCh (Surgical Oncology),
Consultant Robotic Onco Surgeon Apollo Hospitals,
Jubilee Hills, Hyderabad

Dr Bala Vikas Kumar
Dr Thajammul Samrin
Dr Navya Sai Sunkara

Gynaecologic oncology is a specialised field of medicine focused on diagnosing and treating cancers of the female reproductive system, including cervical, ovarian, uterine, vaginal, and vulvar cancers. Over recent decades, advancements in medical technology have significantly improved the management and outcomes of these conditions.

The Emergence of Robotic Surgery:

What is Robotic Surgery?

Robotic surgery utilises advanced robotic systems, composed of several key components:

Robotic Arms -Operated by the surgeon to mimic delicate human hand movements.

-Surgeon Console - Where the surgeon sits and controls the arms, achieving precise manipulation of surgical instruments.

- 3D High-Definition Camera - Provides a magnified view of the surgical site, enhancing visibility and precision.

Benefits of Robotic Surgery in Gynecologic Oncology:

Minimally Invasive:-

- Reduced blood loss,Lower infection risk,Smaller scars for the patient.
- Enhanced Precision and control
- Improved Visualisation
- Better Surgical outcomes.
- Shorter hospital stays.
- Faster Recovery Times:
- Reduced Complications:

Risks and Complications of traditional surgery over robotic surgeries

- Higher risks of infection, bleeding, and damage to surrounding organs.
- Greater potential for postoperative complications, such as blood clots and hernias.
- Longer anaesthesia time, increasing the risk of anaesthesia-related complications.

Limitations in Precision and Recovery:

- Limited precision in removing tumours while preserving healthy tissue.
- Difficulty in accessing deep pelvic structures, impacting surgical effectiveness.
- Longer recovery times due to extensive tissue damage, leading to prolonged hospital stays and delayed return to normal activities.

Recent Data and Statistics on Gynaecological Oncology Cases in Robotic Surgery

Clinical Improvements and Success Rates

- A 2022 study reported that patients undergoing robotic hysterectomy for endometrial cancer had a 10% lower complication rate compared to those undergoing laparoscopic surgery.

- Five-year survival rates for patients undergoing robotic-assisted surgery for cervical cancer were found to be comparable, if not superior, to traditional surgery.

Adoption Rates and Trends:

Robotic surgery adoption continues to grow globally:

- In the United States, robotic-assisted procedures increased by 18% annually from 2015 to 2020.

- Hospitals in Europe and Asia are rapidly integrating robotic systems, driven by their benefits and improved patient outcomes.

Case Studies of Robotic Gynaecological Oncology: Success Stories

Case 1: Robotic Surgery for Advanced Ovarian Cancer

A 55-year-old woman with advanced ovarian cancer underwent robotic-assisted cytoreductive surgery. The minimally invasive approach allowed precise removal of tumour deposits while preserving vital structures. The patient experienced less postoperative pain, minimal blood loss, and a faster recovery compared to traditional open surgery. She was discharged within a week and resumed normal activities shortly after. This case highlights the benefits of robotic surgery in managing complex ovarian cancer cases [oai_ citation: 1,Trends and survival outcomes of robotic, laparoscopic, and open surgery for stage II uterine cancer | International Journal of Gynecologic Cancer](https://ijgc.bmj.com/content/30/9/1347).

Case 2: Robotic Hysterectomy for Endometrial Cancer

A 60-year-old woman diagnosed with early-stage endometrial cancer opted for a robotic-assisted total hysterectomy. The robotic approach provided enhanced visualisation and precision, resulting in a complete resection of the cancer with clear margins. The patient had minimal postoperative pain and a quick recovery, returning home within two days post-surgery. Her follow-up showed no signs of recurrence, demonstrating the efficacy of robotic surgery in endometrial cancer treatment [oai_ citation:2,Trends and survival outcomes of robotic, laparoscopic, and open surgery for stage II uterine cancer | International Journal of Gynecologic Cancer](https://ijgc.bmj.com/content/30/9/1347) [oai_ citation: 3,Trends in the diffusion of robotic surgery in prostate, uterus, and colorectal procedures: a retrospective population-based study | Journal of Robotic Surgery](https://link.springer.com/article/10.1007/s11701-020-01102-6).

Case 3: Robotic Surgery for Cervical Cancer

A 45-year-old woman with stage IB cervical cancer underwent a robotic radical hysterectomy. The surgery was performed with high precision, ensuring the removal of all cancerous tissues while minimising damage to surrounding organs. The patient benefited from reduced blood loss, fewer complications, and a shorter hospital stay. Her recovery was swift, and she returned to her daily activities within two weeks. The patient remained disease-free at her one-year follow-up, showcasing the potential of robotic surgery in cervical cancer treatment [oai_ citation:4,Trends and survival outcomes of robotic, laparoscopic, and open surgery for stage II uterine cancer | International Journal of Gynecologic Cancer](https://ijgc.bmj.com/content/30/9/1347).

Case 4: Robotic-Assisted Lymphadenectomy for Vulvar Cancer

A 65-year-old woman with vulvar cancer required a bilateral inguinal lymphadenectomy. The robotic-assisted approach allowed for meticulous dissection and removal of lymph nodes with minimal incision size, reducing the risk of lymphedema and infection. The patient experienced a quick recovery and significant improvement in quality of life post-surgery. Her successful outcome underscores the advantages of robotic surgery in performing complex lymphadenectomies [oai_ citation:5,6]

These cases illustrate the transformative impact of robotic surgery in gynaecological oncology, providing patients with less invasive options, reduced complications, and faster recoveries.The crux is though we are elaborating our few case scenarios but world wide studies are going including ours and we delighted to contribute the society to

give better outcome by this advance technology and lesser complication rates.

Technological Advancements:

The field of robotic surgery has seen considerable innovations, with new systems offering improved dexterity and a greater range of motion. Here are some of the latest robotic surgical systems known for these advancements:

New Robotic Surgical Systems with Improved Dexterity and Motion Range

1. **Da Vinci 5 Surgical System**

- **Manufacturer:** Intuitive Surgical
- **Features:**
- **Enhanced Instrumentation:** Offers a greater range of motion with improved instrument dexterity.
- **Advanced Ergonomics:** Features a movable overhead boom for optimal surgical site access.
- **Integrated Imaging:** Allows seamless integration with advanced imaging technologies, improving visualisation.
- **Flexibility:** Suitable for multi-quadrant surgeries, making it versatile for complex procedures.

2. **Versius Surgical Robotic System**

- **Manufacturer:** CMR Surgical
- **Features:**
- **Modular Design:** Individual arm units can be positioned around the patient, providing flexibility and tailored setups.
- **Wristed Instruments:** Mimics the human wrist, offering natural dexterity and precision.
- **Compact Footprint:** The small, modular design allows for easy setup and efficient use of operating room space.
- **Enhanced Surgeon Console:** Features a state-of-the-art console with 3D visualisation and ergonomic controls.

3. **Hugo™ Robotic Assisted Surgery System**

- **Manufacturer:** Medtronic
- **Features:**Portable and Modular: Provides flexibility in setup and can be easily moved between operating rooms.

  Advanced Instrumentation: Includes robotic instruments with enhanced dexterity, capable of precise movements.

  Integrated Video and AI: Incorporates advanced imaging and artificial intelligence for better surgical planning and real-time assistance.
- **Data-DrivenInsights:** Offers comprehensive data management tools to track and optimise surgical performance.

4. **Senhance™ Surgical System**

- **Manufacturer:** Asensus Surgical (formerly TransEnterix)
- **Features:**
- **Eye-Tracking Camera Control:** Allows the surgeon to control the camera with their eye movements, enhancing efficiency.
- **Haptic Feedback:** Provides tactile sensation, giving surgeons a sense of touch and improved control over instruments.
- **Scaled Movements:** Offers precise control with motion scaling, translating larger hand movements into smaller instrument movements.
- **Laparoscopic-Like Setup:** Familiar to laparoscopic surgeons, reducing the learning curve and increasing

comfort.

5. **Single-Port SP™ Surgical System**

- **Manufacturer**: Intuitive Surgical (extension of the Da Vinci platform)
- **Features**:
- **Single-Port Access**: Designed for single-incision surgeries, reducing scarring and improving cosmetic outcomes.
- **Flexible Instruments**: Allows for multiple flexible instruments through a single access point, offering unparalleled dexterity.
- **Compact Design**: Facilitates a streamlined workflow in the operating room.
- **Expanded Reach**: Suitable for a variety of complex surgical procedures including those in confined spaces.

Recent Innovations in Robotic Surgery:

New robotic systems with improved dexterity and motion range.

Integration of AI to aid in intraoperative decision-making.

Integration with Other Technologies:

Robotic surgery increasingly incorporates other advanced technologies:

- AI and Machine Learning: Assist in preoperative planning and real-time intraoperative guidance.

Challenges and Considerations:

- High Costs and Economic Consideration
- Initial setup costs, ongoing maintenance.
- Training and Learning Curve- Surgeons training programs, learning curve for proficiency
- Accessibility and Global Inequality- Access disparities in different regions, efforts to bridge the gap.

Future Directions

- Potential future advancements.
- Ongoing research and prospective studies.

Conclusion:

These studies underscore the ongoing advancements and benefits of robotic-assisted surgery in gynecologic oncology. Robotic surgery generally offers improved perioperative outcomes, faster recovery times, and comparable oncologic efficacy to traditional surgical methods. Nonetheless, the need for continuous research and long-term data remains crucial to fully understand the broader impact of these advancements.

Incorporating these recent findings into your article will provide a strong evidence base and highlight the dynamic progress in robotic surgery within gynecologic oncology.

Final Thoughts

The transformative impact of robotic surgery in gynecologic oncology underscores a new era of precision and patient- centred care. By continuing to leverage these advancements, we can look forward to even greater strides in the fight against gynecologic cancers, ultimately improving the lives of our patients.

References:

List of Cited Studies and Data Sources

Trends and survival outcomes of robotic, laparoscopic, and open surgery for stage II uterine cancer | International Journal of Gynecologic Cancer] (https://ijgc.bmj.com/content/30/9/1347) [oai_ citation:6,Trends in the diffusion of robotic surgery in prostate, uterus, and colorectal procedures: a retrospective population-based study | Journal of Robotic Surgery] (https://link.springer.com/article/10.1007/s11701-020-01102-6).

PREMALIGNANT LESIONS OF VULVA: A REVIEW

Dr. Sakshi Mishra
MBBS MS
Assisstant Professor
Department of Obgy

Prof. & Dean Dr. Kavita N Singh
(MS, PhD, FICOG)
Professor & Dean,
GMC Bhopal

INTRODUCTION

Premalignant lesions of the vulva are seen in pre- as well as post-menopausal adult women. These lesions lack a typical clinical presentation and often remain undiagnosed till advanced invasive stages. Common vulvar premalignant lesions are vulvar intraepithelial neoplasia (VIN), Paget's disease, and melanoma in situ (MIS).A careful clinical examination and biopsy of suspicious lesions are imperative for accurate diagnosis.

Vulvar intraepithelial neoplasia (VIN)

Vulvar intraepithelial neoplasia (VIN) is a noninvasive squamous lesion that is a precursor of vulvar squamous cell cancer. It exhibits a spectrum of clinical and histopathological manifestations that often causes severe and long-lasting pruritus, pain, and psychosexual dysfunction. Incidence of HPV-associated VIN is on the rise, with the highest frequency in women of 20–35 years.

History of evolution of classification system of VIN:

The term VIN was first introduced in 1982. The International Society for the Study of Vulvovaginal Diseases (ISSVD) subclassified VIN into VIN 1, 2, and 3, respectively, showing mild, moderate, and severe atypia/carcinoma in situ.

The ISSVD in 2004 proposed a two-tiered classification for squamous VIN, including

- VIN, The usual type (uVIN), caused by a persistent infection with high-risk human papillomavirus (HPV).
- VIN, The differentiated type, (dVIN) HPV unrelated , associated with lichen sclerosus (LS).

The uVIN subtype predominantly affects younger women and exhibits a multifocal pattern. The dVIN subtype , although less common (2-5%) has the highest potential for malignancy and it typically affects older women.

A further modification was put forth by ISSVD in 2015 to classify vulvar squamous intraepithelial lesions (SILs) as :

- Low-grade SIL (LSIL) of the vulva (vulvar LSIL, flat condyloma, or human papilloma virus effect)

	Classification
HPV-Associated Squamous Intraepithelial Lesions	• Low-grade squamous intraepithelial lesion of the vulva. • High-grade squamous intraepithelial lesion of the vulva.
HPV independent VIN`	• Differentiated vulvar intraepithelial neoplasia. • Differentiated exophytic vulvar intraepithelial lesion Vulvar acanthosis with altered differentiation.

HPV, human papillomavirus; VIN, vulvar intraepithelial neoplasia

- High-grade SIL of the vulva (vulvar HSIL, uVIN)
- dVIN

The 2020 World Health Organization tumor classification:

The 2020 WHO tumor classification divides vulvar lesions into the following two categories: "HPV-associated squamous intraepithelial lesions" and "HPV independent VIN" (Table 1).

Other Treatment Options

HPV, human papillomavirus; VIN, vulvar intraepithelial neoplasia

ETIOLOGY:

The association between HPV and vulvar neoplasia was reported for the first time by Charlewood and Shippel in 1953. The prevalence of HPV in VIN ranges from 72% to 100% and is strongly associated with uVIN. HPV 16 is the most common type (77.2%) followed by HPV 33 (10.6%) and HPV 18 (2.6%).

HPV viral DNA integrates into host cells, resulting in the production of oncoproteins E6 and E7 which interfere with normal cellular function. HPV E6 can interact with the tumor suppressor gene p53, leading to p53 dysfunction and consequently absence of cell cycle arrest . HPV E7 can inactivate the retinoblastoma tumor suppressor gene pRb, which results in overexpression of the cell cycle related biomarkers p16ink4a and p14arf, and hyperproliferation of infected cells . As a result, most uVIN lesions are positive for p16ink4a and p14arf, but p53 negative .

dVIN shows de novo tumor suppressor protein (p53) genetic alterations unrelated to HPV. Mutations in p53, phosphatase, and tensin homologue tumor suppressor gene and microsatellite instability are demonstrated in HPV independent carcinogenesis. Loss of expression of the tumor suppressor GATA-binding protein 3 (GATA3) is seen in all SCC associated with uVIN and in 81% of those associated with dVIN. GATA3 immunohistochemistry along with p53 may be a useful tool in accurate diagnosis of VIN.

Vulvar carcinogenesis and severity thereof are associated with DNA methylation, emphasizing the potential of DNA methylation biomarkers in the diagnostic workup of VIN.[9]

RISK FACTORS:

- Multiple sexual partners
- HPV infection, particularly high-risk strains.
- Smoking.
- Immunosuppression.
- Chronic vulvar dermatoses (e.g., lichen sclerosus, lichen planus).

Clinical features

uVIN is seen on hair bearing areas of labia majora and appears as a raised, well-demarcated asymmetrical whitish to erythematous plaque [Figure 1]. It may be asymptomatic or may present with pruritus, pain, burning, and dysuria.

dVIN presents as a unifocal, rough surfaced, gray-white discoloration, or an erythematous lesion with or without ulceration; occasionally, it can present as ill-defined whitish plaques. It is often associated with LS and LP. Early detection and proactive management of LS may reduce the risk of VIN.

Figure 1: Usual vulvar intraepithelial neoplasia (high-grade squamous intraepithelial lesion) showing, indurated plaque involving the left labia and whitish plaques near the fourchette and labial commissure.

Differential diagnoses

- Condyloma acuminata
- Condyloma lata
- Lichen simplex chronicus
- LS, LP
- Vulvovaginal candidiasis (vvc),
- Paget's disease of vulva.

DIAGNOSIS:

Clinical Examination: A thorough examination of the vulva, perineum, perianal, and anal regions, including the cervix and vagina.

Colposcopy:

- Indicated in subclinical lesions with persistent pruritus and pain.
- Helps to identify additional lesions in lower genital tract and perineal area.
- Acetic acid or Lugol's iodine may be applied to highlight abnormal areas.

Dermoscopy:

- Helps to differentiate infective and inflammatory conditions of the vulva.
- The recognition of specific dermoscopic patterns may improve the diagnostic accuracy in early phase vulvar diseases.
- uVIN - numerous white dots surrounded by glomerular vessels with irregular patchy distribution. Focal structureless, bluish-brown areas, and peripheral gray-blue/brownish dots arranged in a linear fashion.
- dVIN- pink to red, structureless, background with red areas due to superficial erosions and vascular structures (consisting of curvy, short, serpentine, and dotted vessels).

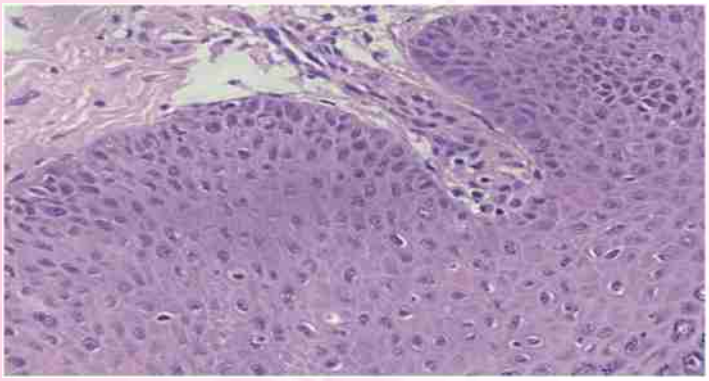
Histopathology:

Indications for biopsy include:

- Any vulvar lesion not responding to empiric therapy
- Rapid change in color, size, and border
- Suspected condyloma which is resistant to topical therapy
- Post-menopausal women with apparent genital warts.

Multiple lesions may need multiple biopsies.

uVIN : Epidermal hyperkeratosis and parakeratosis. There is loss of cell maturation with nuclear hyperchromasia,



Histological sections reveal acanthosis with nuclear atypia and increased mitotic activity involving the lower two-thirds of the epithelium, suggestive of VIN

high nuclear-to-cytoplasmic ratio, pleomorphism, and numerous mitotic figures at all levels of the epidermis. Warty type shows papillomatous projections with wide and deep rete ridges.

Basaloid type has flat surface with diffuse proliferation of small, undifferentiated, basaloid cells.

mixed VIN has manifestations of both basaloid and warty patterns.

dVIN : Epidermal hyperplasia with parakeratosis and atypical keratinocytes restricted to basal and parabasal layers. Nuclear pleomorphism, hyperchromatism, and mitoses are seen. Macronuclei and angulated nuclei are most specific for dVIN and useful to differentiate it from the reactive nuclear enlargement seen in LS and non-neoplastic epithelial disorders.

Staining with MIB1 and p53 is helpful to differentiate dVIN from normal epithelium.

Immunohistochemistry

dVIN : p53 positive and p16 negative

uVIN : p53 negative and p16 positive.

In a study by Takacs et al., all VIN and vulvar cancers were sec62/ki67 and p16/ki67 dual stain positive whereas normal cells and LSILs stained negative.

TREATMENT:

The treatment of premalignant lesions of the vulva, or vulvar intraepithelial neoplasia (VIN), aims to eliminate the lesions, relieve symptoms, and prevent progression to invasive cancer. Treatment modality depends on the type, size, number, location, extent of the disease, and risk of invasivE malignancy. Treatment options in uVIN include wide local excision, vulvectomy, laser abation, topical treatment, photodynamic therapy (PDT), and therapeutic HPV vaccination.

Surgical excision is the treatment of choice in dVIN.

Wide Local Excision:

Wide excision including 1 cm normal margin is indicated in raised, ulcerated lesions with irregular borders. Positive epithelial margins are a risk factor for recurrence. Removal up to underlying dermis helps to prevent early invasive disease.

Skinning vulvectomy

may help when topical treatments, laser ablation, and smaller excisions fail.

also the treatment option in multifocal, large VIN lesions with extensive involvement.

Here, vulvar skin is removed along a relatively avascular plane beneath the epidermis, preserving the subcutaneous tissue.

Laser ablation

Laser ablation is preferred in non-hair bearing areas and is attempted for single as well as multiple or confluent lesions.

Recurrence rates are comparatively higher.

Carbon dioxide (CO_2) laser surgery permits outpatient treatment under local anesthesia with excellent cosmetic and functional results.

Argon beam coagulation has also been tried in uVIN.

Topical treatment

The major advantage of topical treatment is the preservation of vulvar anatomy and function.

Imiquimod:

- Acts by binding to toll-like receptors on the cell surface of dendritic cells and inducing secretion of pro-

inflammatory cytokines. It has antiviral and antitumor properties.

- Gradual escalation in doses is advised (once a week for 2 weeks, twice weekly for 2 weeks, followed by thrice a week). Minimum 16 weeks of treatment is recommended.
- Complete response rates range from 5% to 88%.
- Recurrence rate is 27%.

Topical 5-Fluorouracil (5-FU)

5-FU is useful in uVIN and has up to 74% success rate.

It causes burning, pain, edema, and ulceration, and is poorly tolerated.

Cidofovir : Cidofovir is a nucleoside analog with antiviral properties.

Combined therapy

Combined treatment with superficial shaving and 5-amino levulinic acid-PDT may be a safe and effective option in women with VIN who want to preserve their vulvar architecture; especially in those with large, multifocal, high grade lesions and in repeated recurrences.

Newer Modalities of Treatment:

1. **Photodynamic Therapy (PDT):**

- PDT involves the application of a photosensitizing agent to the lesion, followed by exposure to a specific wavelength of light.
- It causes selective destruction of abnormal cells while sparing healthy tissue.
- Benefits are minimal scarring and preservation of vulvar anatomy and function.

2. **Biological and Immunotherapy:**

HPV vaccination : Prophylactic Quadrivalent vaccine HPV vaccines reduce premalignancies and malignancies and is found to decrease the risk of VIN.However, evidence for efficacy of HPV vaccine in the treatment of VIN is insufficient and is of low quality.

Research is ongoing into therapeutic vaccines targeting existing HPV infections.

Immune Checkpoint Inhibitors: Investigational use of drugs that enhance the immune system's ability to recognize and attack cancer cells. Examples include PD-1 inhibitors like pembrolizumab.

3. **Targeted Therapy:**

Targeted therapies aimed at specific molecular pathways involved in VIN are under investigation. These therapies may offer more precise treatment options with fewer side effects compared to traditional methods.

Follow-Up and Surveillance:

Regular follow-up is crucial to monitor for recurrence or progression. This typically includes clinical examinations and, when necessary, repeat biopsies or imaging studies.The choice of treatment depends on several factors, including the extent and location of the lesion, patient preferences, and the presence of any underlying conditions. A multidisciplinary approach involving gynecologists, dermatologists, and oncologists may be beneficial for optimal management of VIN.

PAGET'S DISEASE OF THE VULVA

Extramammary Paget's disease (EMPD) is a rare, premalignant, intraepithelial adenocarcinoma. Vulva is the most common site affected. The WHO defines vulvar Paget's disease (VPD) as "An intraepithelial neoplasm of epithelial origin expressing apocrine or eccrine gland-like features and characterized by distinctive large cells with prominent cytoplasm referred to as Paget's cells." VPD can be primary disease, arising on the vulva or secondary, arising from a malignancy of gastrointestinal tract or urogenital tract. VPD is seen between the sixth and eighth decades of life with a mean age of 65 years.

Clinical features

multifocal and asymmetrical.

pruritus, burning, pain, and edema.

The primary lesion can be an erythematous, scaly plaque or weepy, crusty erosions, and ulcerations. Hypo or hyperpigmentation, infiltrating nodules, and vegetative lesions with lymphadenopathy may also occur.

Scattered areas of erosion and white scale gives "strawberries and cream" appearance.

"underpants-pattern erythema."

It has an ominous prognosis with rapidly fatal distant metastases. [37]

Investigations

Dermoscopy

- Presence of thick polymorphic vessels diffusely arranged throughout a pinkish-red background with milky red areas.
- Presence of dotted glomerular vessels.

Histopathology

- Paget's cell is the pathognomonic cell found in the epidermis, mostly near the basement membrane zone.
- Epidermal acanthosis, parakeratosis, and hyperkeratosis.

Immunohistochemistry

- Primary EMPD : positive for cytokeratin (CK)7 and gross cystic disease fluid protein-15 (GCDFP-15) and negative for CK20.
- Secondary EMPD is CK20 positive and negative for both CK7 and GCDFP-15.
- Serum carcinoembryonic antigen (CEA) in invasive EMPD.
- CK19 fragment 21-1 (CYFRA 21-1) is used to assess disease progression and treatment efficacy in EMPD.
- Screening for genitourinary, gastrointestinal, and breast diseases is warranted in VPD.

Treatment

- Surgical procedures : (Mainstay) local excision, simple or radical vulvectomy
- Conservative approach: CO2 and neodymium-doped yttrium aluminum garnet lasers, PDT alone or in combination with other modalities .
- Topical: 5% imiquimod cream, 5-FU, and bleomycin .
- Radiation therapy and chemotherapy .
- Targeted therapy with trastuzumab is a new treatment for VPD showing overexpression of human epidermal growth factor receptor-2.

Prognosis:

Presence of dermal invasion, elevated CEA levels, presence of nodules in the primary lesion, and bilateral lymph node metastases are bad prognostic factors.

MELANOMA IN SITU

MIS is rare on the vulva, but has a definite risk of progression to invasive melanoma. Hence, all doubtful pigmented lesions of the vulva should be biopsied. If melanoma is suspected, excisional biopsy with 5 mm clinically normal margin of skin is recommended, as it can be curative too.

CONCLUSION

The incidence of vulvar premalignancies, especially VIN, is increasing; so gynecologist/dermatologists should approach any atypical vulvar lesion with suspicion. Early diagnosis is of utmost importance to prevent invasive malignancy. Treatment is best accomplished by an interdisciplinary approach. Lifelong surveillance is essential as recurrences are common in all vulvar premalignancies.

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MIMANSA MONTHLY QUIZ 3

1) 1.Which of the following tumors is LEAST likely to be hormonally active:

A. Sertoli-lyedingcelltumor. B. Granulosa cell tumor.
C. Fibroma. D. Thecoma.

2) 16 year old single girl presented with a mass in the pelvis was detected clinically all the following investigation can be done , EXCEPT :

A. CT B. Laparoscopy
C. PAP smear D. MRI

3) The prevalance of HPV in VIN(Vulval intraepithelial neoplasia) is

A) 72-100% B) 7-10%
C) 35-40% D) 2-3%

4) False regarding CERVAVAC vaccine

A) Should be injected intravenously
B) 2 doses are recommended to individuals between 9 to 14 years of age.
C) It is a quadrivalent vaccine.
D) It is developed by serum institute of india.

5. In patients with endometrial hyperplasia with atypia all are true except

A) The risk of progression to invasive malignancy- as high as 27.5% if not treated.
B) Hystrectomy is curative & preferred treatment
C) Possibility of coexistent endometrial malignancy in atypia is around 43% of cases.
D) Endometrial ablation,morcellation or supracervical hysterectomy should be performed

6) Suggestive ultrasound features of ovarian malignancy include following EXCEPT :

A. Bilateral B. Presence of ascites
C. Unilocular D. Capsule integrity is disrupted with projection

7) A ratio of CA125 and CEA more than 25:1 favours :

A. Primary ovarian malignancy B. Secondary ovarian malignancy
C. both D. none

8) Reids colpscopy score -

A) 0-2 likely to be CIN 1
B) It includes margins, colour, and vessels of acetowhite lesion
C) 6-8 corresponds to CIN 3
D) All of the above

9) Choose one best answer

A) Risk Reducing salpingo-oophorectomy (RRSO) is recommended at age 35-40 for women with BRCA1 mutaion.
B) RRSO can be delayed till age 50-60 in patients with BRCA 2mutation.
C) OCP,s are contraindicated in patients with BRCA1 and BRCA2 mutation.
D) All of the above

10) Endometrial adenocarcinoma is most often preceded by:

A. Cystic hyperplasia.
B. Endometrial hyperplasia.
C. Endometrial hyperplasia with cytological atypia.
D. Arias-stella phenomena.

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