Chapter 49
Vaginal Preinvasive Lesions and Vaginal Cancer

Describe main features and characteristics of vaginal intraepithelial neoplasia (VaIN).

- Vaginal squamous epithelial cells have abnormal mitosis, abnormal maturation, and nucleus aneuploidy (irregular nuclear contours and chromatin clumping, nuclear enlargement).
- The lesion is limited to the vaginal epithelium and the basal membrane is intact.
- It is precancerous lesion.
- It is less common than cervical and vulvar intraepithelial lesions.
- The pathophysiology is not known clearly.
- For similar etiological reasons, it may be associated with cervical intraepithelial neoplasia (CIN) and vulvar intraepithelial neoplasia (VIN).
- The actual incidence is unknown (<1/100,000).
- It is between the ages of 43 and 60 years.
- Human papilloma virus (HPV) is the most important risk factor.

What are the risk factors of VaIN?

- The most important risk factor for lower genital tract neoplasia is the presence of HPV infection.
- HPV 16 and 18 are responsible for most lesions.
- Other risk factors:
  - Low education level and low family income
  - Advanced age
  - Vaginal condyloma or CIN history
  - Polygamy
  - Risky sexual intercourse
  - Cigarette
  - Pelvic radiotherapy

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  - Presence of immunosuppression such as human immunodeficiency virus (HIV) infection
  - Intrauterine diethylstilbestrol (DES) exposure

- 50–90% of patients with VaIN are associated with cervical or vulvar premalignant lesions/neoplasia.
- In patients with CIN III, 5% (1–7%) VaIN can be detected.
- Some high-grade VIN or VaIN lesions may be caused by high-grade or malignant cervical disease.

Describe the etiology of VaIN.

- Lesions that extend into the vagina in CIN and cannot be detected.
- Isolated lesions may develop de novo (multifocal lesions).
- The cervix, vagina, and vulva with similar histological structure are exposed to the same carcinogenic agents → Multicentric neoplasms (50% of women with VaIN have concurrent vulvar or cervical neoplasia).
- Coitus/tampons use → Erosion zones → Recovering metaplastic areas → Persisted HPV infection → Neoplasia
- Unlike cervix, the vagina epithelium is more stable and VaIN is rarer.
- In women with DES exposure, squamous metaplasia is more common. This explains the increased risk of VaIN.

Explain VaIN's clinic.

- It is usually asymptomatic.
- Postcoital and/or postmenopausal bleeding.
- There may be bloody vaginal discharge sometimes due to superimposed vaginal infections.
- In 50% of the patients, the lesion is multifocal.
- 90% of patients with VaIN have CIN (multicentric).
- If there are no identifiable cervical lesions or abnormal smear findings after hysterectomy, VaIN should be excluded.
- The most common location is vaginal 1/3 proximal posterior wall (57–83%).
- In 31% of patients, it is caused by the lower 1/3 part of the vagina.
- According to the VaIN epithelium involvement:

  - VaIN I (lower 1/3): between pillows, ovoid, puffy from the surface.
  - VaIN II (up to 2/3): Acetone white becomes prominent, thicker, and limited lesion.
  - VaIN III, CIS (carcinoma in situ) (almost or full layer): papillary structure, punctuations, and mosaic vascular structure.

Describe the diagnosis of VaIN.

- Vaginal touch is required to assess vaginal wall thickening and irregularity.
- Detailed colposcopic examination (acetic acid and lugol) and, if necessary, vaginal biopsy are performed.
- Partial closure of the speculum during biopsy facilitates the procedure.
- After topical estrogen treatment in the menopause, the lesions become more visible.

Describe the treatment of VaIN.

- Premalignant potential is lower than CIN.
- VaIN I often regresses spontaneously.
- There is no malignant potential. It is multifocal and has a tendency to recur after treatment. No treatment required.
- Treatment options:
  - Topical treatment (5-FU (fluorouracil), imiquimod): large or multifocal lesions
  - Ablation (laser, cryo/cautery): depth of invasion to the tissue should be considered.
  - Excision: (local excision, partial or total vaginectomy)
  - Radiotherapy: intracavitary, rarely used.
- History of unsuccessful treatment, multifocal disease, additional diseases of the patient, and sexual function is important in the choice of treatment.
- Ablative therapies are an option if the lesion is completely seen and invasion is excluded by biopsy.
- VaIN II → Ablative treatment (laser).
- VaIN III → 2–8% progress to invasive cancer or with 28% invasive cancer → Excision required.
- Follow-up after treatment
  - Smear + HPV test should be performed at 6 months/1 year intervals.
  - Colposcopy if anyone is abnormal.
  - Long-term follow-up is required.
- HPV vaccine, smoking cessation, treatment of other lesions may prevent the development of VaIN.

49.1 Vaginal Cancer

Describe the main features of the vaginal cancer.

- 80–90% of vaginal cancer is seen as metastasis of other cancers (cervix, endometrium, ovary, GIS, breast, GTN, colorectal, vulva, urinary system).
- Primary vaginal cancer is rarer and usually originates from the vaginal epithelium.
- 2% of all genital system cancers.
- In situ or invasive vaginal cancer is seen in approximately 1/100,000 ratio.
- It is usually seen in postmenopausal women (mean age 60 years).
- It is associated with HPV (HPV 16 and 18 are positive in 50% of patients).
- Other risk factors: low socioeconomic status, lifetime sexual partner, early coitus, smoking, chronic vaginal irritation, history of abnormal Pap smear, history of cervical cancer, history of radiotherapy (RT), intrauterine DES exposure.
- In 50% of cases, there is a cervical cancer.

- In women with CIN III, the risk of developing vaginal cancer increases by 6.8 times.

Describe the clinic for vaginal cancer.
- 1/5 of women are asymptomatic at the time of diagnosis.
- Vaginal discharge (watery, bloody, or smelly vaginal discharge).
- Painless vaginal bleeding.
- Findings related to adjacent organ involvement (polyuria, hematuria, tenesmus, melena, constipation).
- Vaginal mass from the hand.
- Five percent of the patients have pelvic pain due to their spread to the surrounding tissues.
- It usually spreads through the neighborhood by direct invasion. It can also spread through lymphatic and hematogenous routes.

What are the histological types of primary vaginal cancer?
- Squamous cell carcinoma (epidermoid type) (80–90%).
- Adenocarcinoma (9%),
- Melanoma (3–5%)
- Sarcoma (3%),
- Others (undifferentiated, small cell carcinoma, lymphoma, carcinoid) (2%),

What are the main features of the squamous cell carcinoma of the vagina?
- It is the most common type. HPV is related. It is seen around the age of 60 years.
- Lesions can be ulcerative, indurated, endophytic, or exophytic.
- Verrucous carcinoma is a rare squamous cell carcinoma variant with well-differentiated and low malignant potential.
- Locally aggressive, rarely metastasis.
- It can reach big sizes.
- It consists of large papillary leaves covered with histologically dense keratin.

What are the main features of the adenocarcinoma of the vagina?
- It is generally seen as a metastasis of colon, endometrium, ovarian, stomach, and pancreatic cancers.
- The primary adenocarcinoma is rare.
- Almost all cases of primary vaginal cancer under 20 years of age are adenocarcinoma.
- It may develop from vaginal adenosis, wolffian canal residues, periurethral gland, and endometriotic foci.
- Clear cell carcinoma is an adenocarcinoma that develops on the basis of vaginal adenosis in young women with intrauterine DES exposure.
- At diagnosis, 70% is stage I.
- It is usually caused by the front wall of the vagina.
- Intrauterine exposure for the first 12 weeks is the highest risk.
- Intrauterine DES exposure also increases the risk of invasive/in situ squamous cell cancer in the cervix (5.4 times).
- DES-associated vaginal cancer is seen at a mean age of 19 years (7–33 years).

- The first gynecological examination of women exposed to DES; cervical and vaginal cytology, palpation, and colposcopic evaluation should be performed.
- Clear cell carcinoma treatment with primary surgery and/or RT results is good.
- The prognosis of other adenocarcinomas is worse.

What are the main features of the sarcoma of the vagina?

- Primary sarcomas seen in the vagina: leiomyosarcomas, endometrial stromal sarcomas, malignant mixed Müllerian tumors, and rhabdomyosarcomas.
- The most common embryonal rhabdomyosarcoma (sarcoma botryoides) is seen (the most common malignant mesenchymal tumor of the vagina in childhood).
- There is a mass of grape-shaped nodules in the vagina.
- The mean age is 3 years, with poor prognosis.
- It is multimodal treated including surgery, chemotherapy, and RT.

What are the main features of the melanoma of the vagina?

- Vaginal melanomas are rare.
- It originates from mucosal melanocytes or atypical melanocytic hyperplasia.
- The average age is around 60 years (22–84 years).
- The most common symptoms are vaginal bleeding.
- It is more common in Caucasian women.
- It is most common in the vaginal 1/3 distal anterior wall.
- Lesions are usually in the form of non-pigmented blue-black or black-brown mass, plaque, or ulceration.
- Aggressive tumors.
- The 5-year survival rate is <20%.

How is vaginal cancer diagnosed?

- Squamous cell carcinoma is usually located 1/3 proximal, posterior wall of the vagina. During the pelvic examination, it is necessary to pay attention to the bottom of the speculum.
- Diagnostic evaluation:
  - Pelvic examination
  - Vaginal cytology
  - Colposcopy
  - Vaginal biopsy
- Pelvic examination should include a bimanual examination, palpation of the masses on the vaginal wall, palpation of the inguinal lymph node, and rectovaginal examination.
- Vaginal cytology.
- Vaginal colposcopy should be performed with acetic acid followed by Lugol dye.
- Vaginal biopsy can be performed under anesthesia if necessary.
- Imaging methods for staging: evaluation by thorax and skeletal radiography.

- Computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET-CT) can also be used if necessary.
- The diagnosis is made by vaginal biopsy.
- Other genital pathologies (menopausal vaginal atrophy, vaginal infection, and trauma) that cause vaginal bleeding in differential diagnosis should be excluded by pelvic examination.
- Benign causes (vaginal polyps, Gartner canal cyst, vaginal adenosis, and endometriosis) should be excluded in the presence of vaginal mass.

Describe ways of spreading vaginal cancer.
- Direct extension to pelvic soft tissue: vulva, cervix, bladder, rectum, other pelvic organs
- Lymphatic: from the upper 1/3 vagina to the pelvic/para-aortic lymph nodes, from the lower 1/3 vagina to the inguinal and femoral lymph nodes
- Hematogenous: lung, liver, and bone.

How is staging of vaginal cancer done?
- Clinical staging system is used (The International Federation of Gynecology and Obstetrics (FIGO)).
- Clinical staging:
  - Physical examination, cystoscopy, proctoscopy, chest and skeletal radiography are based on the findings.
  - Biopsy of the inguinal/femoral or other lymph nodes or the results of fine needle aspiration can be included in clinical staging.
- At the time of diagnosis, 26% of the patients were stage I, 37% were stage II, 24% were stage III, and 13% were stage IV.
- **Staging**
  - Stage 0 → In situ cancer, VaIN III.
  - Stage I → Cancer limited to the wall of the vagina.
  - Stage II → Cancer kept the vaginal tissue, but did not reach the pelvic wall.
  - Stage III → Cancer has reached the pelvic wall.
  - Stage IVA → The cancer was directly spread out of the true pelvis and/or kept the bladder/rectum mucosa (bullous edema does not do the stage IV).
  - Stage IVB → Cancer has spread to distant organs.

What are the important prognostic factors of the vaginal cancer?
- Tumor stage, location, and size are important prognostic factors.

What are the treatment options of the vaginal cancer?
- Treatment options: surgery, RT, and chemo-radiotherapy.
- In the choice of treatment: the stage of the tumor, negative surgical margin and the patient's sexual function is important.

In which situations surgical therapy of the vaginal cancer is chosen?
- In stage I, if the tumor is 1/3 in the vagina; Radical hysterectomy + upper vaginectomy (>1 cm surgical margin) + bilateral pelvic lymphadenectomy.

- If there is no uterus; radical upper vaginectomy + bilateral pelvic lymphadenectomy.
- Young patients who need radiotherapy; laparoscopic ovarian transposition + surgical staging + bulky lymph node resection should be performed.
- If there is a rectovaginal/vesicovaginal fistula in patients with stage IVA cancer; pelvic lymphadenectomy + pelvic exenteration.
- If there is a central recurrence after RT; pelvic exenteration (Evidence C).

In which situations radiotherapy is chosen?
- It is difficult to obtain negative surgical margins in large tumors.
- In addition to inguinal lymph node dissection, vulvovaginectomy is often required in middle/lower vaginal involvement. Therefore, surgery is not a good option.
- In stage I patients, RT is more effective if the tumor diameter is >2 cm or there is middle/lower vaginal involvement.
- Vaginal lower 2/3 part involvement; inguinal lymph nodes should be dissected or given RT (Evidence C).
- RT alone provides adequate treatment in early stage tumors.
- Adding brachytherapy to external RT increases survival from 3.6 years to 6.1 years.
- A total radiation dose of 70–75 Gy is recommended.
- Small superficial stage I tumor; intracavitary RT.
- Large and thick lesions; intracavitary and interstitial RT before external RT.

In which situations chemo-radiotherapy is chosen?
- In advanced vaginal cancers, surgery or RT has low chances of success.
- Success in stage II–IV patients: Chemoradiotherapy > RT > surgery (52% > 44% > 14%).
- Cisplatin/fluorouracil can be used simultaneously with radiotherapy.
- It is the primary treatment in patients with stage II–IV tumors.
- Recommended for tumors larger than 4 cm in diameter.

In which situations chemotherapy is chosen?
- It is an option in recurrent or advanced cases in which surgery or radiotherapy cannot be performed.
- Neoadjuvant chemotherapy and then radical surgery are a promising alternative. However, it has not been proven yet.
- If there is no treatment option, **palliative care** should be performed.

What are the complications of the vaginal cancer after treatment with surgery and radiotherapy?
- Complications occur in 10–15% of patients after treatment (rectovaginal or vesicovaginal fistulas, radiation cystitis or proctitis, rectal and vaginal stenosis and rarely vaginal necrosis).
- Surgery related urethra, bladder, and rectum injury.
- Vaginal dilators should be used to prevent vaginal stenosis after RT.

What is the ideal follow-up after treatment?

- In patients early stage/without additional treatment:
  - First 2 years; every 6 months
  - Then annually
- In advanced stage/additional treatment patients:
  - First 2 years; every 3 months
  - 3–5 years; every 6 months
  - Then annually
- History and physical/pelvic examination is performed.
- If recurrence is suspected, CT or PET may be taken.

What is the most important factor affecting the prognosis of the vaginal cancer?

- The most important factor affecting the prognosis is the stage of the disease at the time of diagnosis (tumor prevalence, size and depth of invasion).

What are the 5-year disease-free survival rates of the stages of the vaginal cancer?

- 5-year disease-free survival is 85% in Stage I, 78% in Stage II, and 58% in Stage III–IV.

Suggested Reading

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