Evidence Based Management of Vulval and Vaginal Cancers

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Pathology

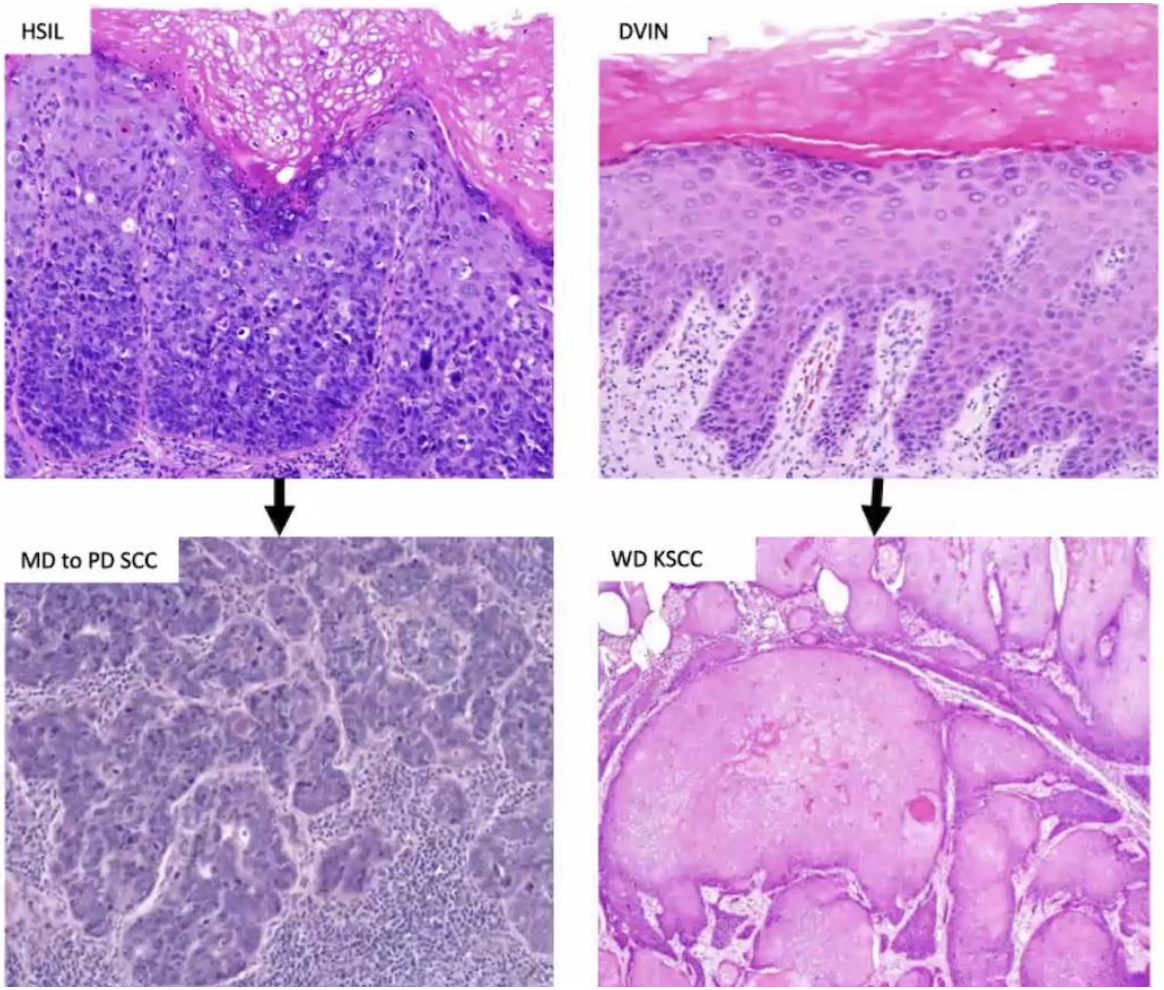
Historically divided into:

- HPV-independent

  Differentiated vulvar intraepithelial neoplasia (DVIN), longstanding dermatoses, verrucous carcinoma -> well differentiated keratinizing SCC

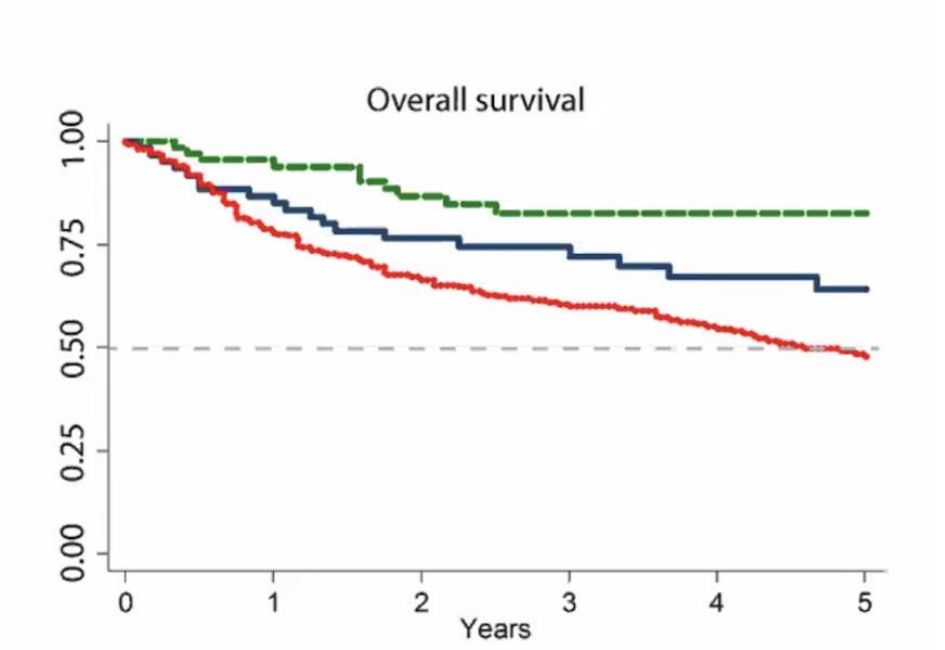
- HPV-dependent

  HSIL (VIN 2/3) --> basaloid SCC



Molecular classification of Vulvar Cancer

HPV associated
HPV independent p53 mutant
HPV independent p53 wild type
myriad of mutationsPIK3CA, NOTCH 1, HRAS



Significant diff in outcomes 5 ys OS

HPV associated 83%
HPV independent;p53 wild type 64%
HPV independent; P53 mutant 48%

IHC should include p16 and p53

2021 FIGO staging for carcinoma of the vulva

Stage I: Tumor confined to the vulva

IA: Tumor size ≤2 cm and stromal invasion ≤1 mm

IB: Tumor size >2 cm or stromal invasion >1 mm

Stage II: Tumor of **any size** with extension to **lower one-third** of the **urethra**, lower one-third of the **vagina**, lower one- third of the **anus** with negative nodes

Stage III: Tumor of any size with extension to upper part of **adjacent perineal structures,** or with any number of nonfixed, nonulcerated lymphnode

IIA: Tumor of any size with disease extension to **upper two-thirds** of the **urethra**, upper two-thirds of the **vagina, bladder mucosa**, **rectal mucosa**, or regional **lymph node metastases ≤5 mm**

IIIB: Regional **lymph node** metastases **>5 mm**

IIIC: Regional lymph node metastases with **extracapsular spread**

Stage **IV:** Tumor of any size **fixed to bone, or fixed, ulcerated lymph node** metastases, or **distant metastases**

IVA: Disease fixed to pelvic bone, or fixed or ulcerated regional lymph node metastases

IVB: Distant metastases

Treatment and Disease outcomes

- Mainstay of management localized vulvar cancer is surgical resection and lymph node assessment

- 5-year OS Limited disease- 86%.

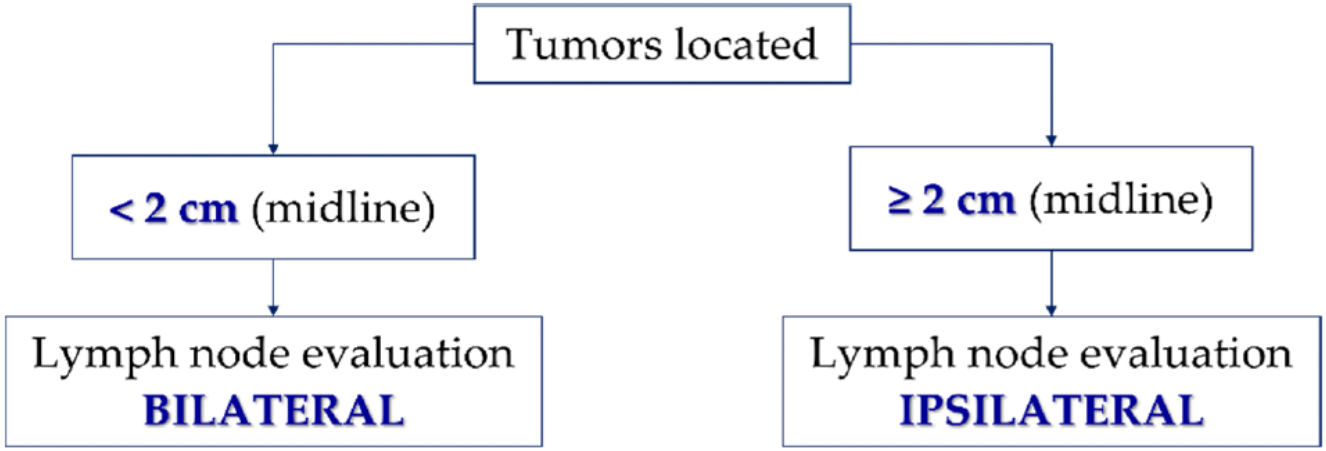
  Regional node metastasis- 54%.

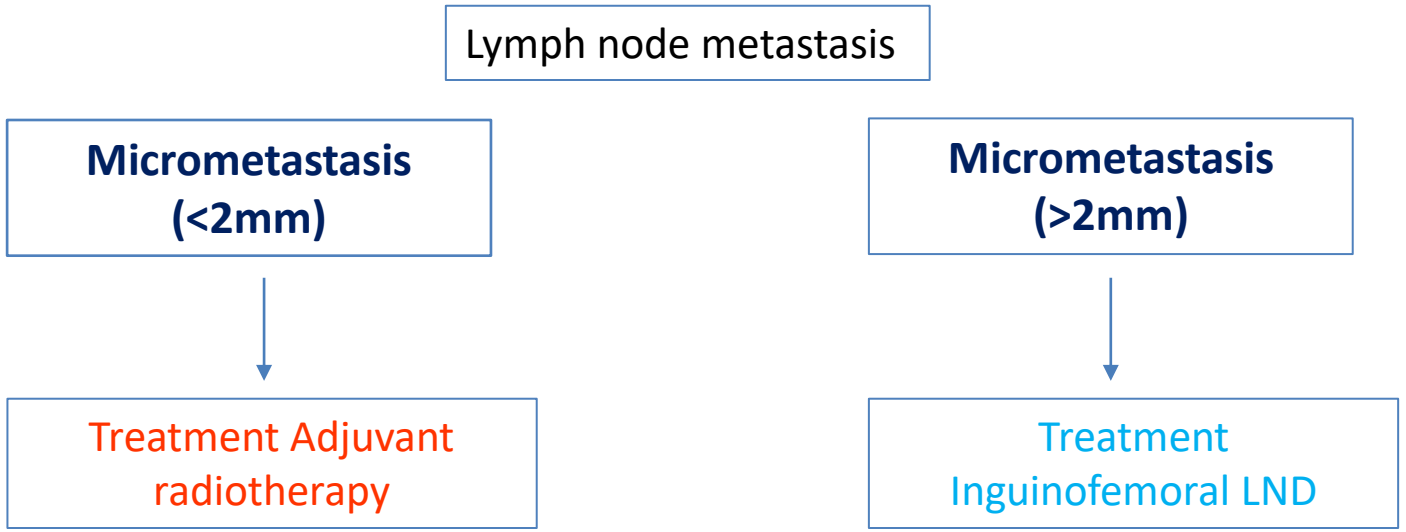
  Metastatic disease-16%

- Radical local excision
- Goal : To achieve a microscopic tumor free margin <8 mm formalin fixed margin (except for tumors close to clitoris urethra, anus), where margins may be compromised.

Management of Groin

- Groin LND can be omitted in tumors < 2cm, depth of invasion< 1mm
- Unifocal tumor <4cm, lateralized **lesions, > 1mm DOI.-SLN Biopsy**
- **Ipsilateral IFLN** If no SLNs are detected
- Positive LN on SLN- **B/L groin dissection**
- **B/L dissection** in tumors within 1cm of **midline structures/ anterior labia minora**
- **IFLND-Superficial and deep femoral LN should be removed**
- **Inadequate LND- negative impact of survival (15 LN for B/L LND,10 LN for Unilateral LND)**


Tumors located
< 2 cm (midline)
≥ 2 cm (midline)
Lymph node evaluation
BILATERAL
Lymph node evaluation
IPSILATERAL


Lymph node metastasis
Micrometastasis
(<2mm)
Micrometastasis
(>2mm)
Treatment Adjuvant
radiotherapy
Treatment
Inguinofemoral LND

Stage I & II- Adjuvant treatment

Risk Factors for local recurrence

Heaps criteria

- (+) margins; Close margin < 8 mm pathologically or < 1 cm clinically
- LVSI
- lesions > 5 mm deep

In addition, Poorly diff tumors esp with infiltrative margins

dVIN in the margin, dVIN+ Lichen sclerosis in the margin, and FIGO stage II or higher disease independently associated with a higher local recurrence rate. (Te Grootenhuis NC,2019)

A Close or positive resection margin is the most important prognostic factor for local recurrence

Positive or close margin

Re-excision

- Adv- avoidance of radiation toxicity esp vag stenosis
- Difficult in midline tumors

Radiotherapy

- 5 yr OS with RT-68%; without RT-29% *(Ignatov et al,2016)*
- Preferred midline tumours esp. in the presence of other risk factors
- **Margins ≤5 mm associated with highest risk of vulvar recurrence**
- **RT dose ≥56 Gy assoc. with lower risk of relapse than ≤50.4 Gy** *(Viswanathan et al, 2013)*

Stage III,IV-A & IV-B

Node positive
Unresectable

LN inv- most important prognostic factor
GOG 37, Homesley et al, 1986
Survival advantage in clinically + groin LN,
>1 groin LN+
nodal ECE

Role of RT in Single LN + ds- controversial
OS declined with each additional positive lymph node.
The most significant difference in survival with adjuvant radiation noted in those with a single positive lymph node (Woelber,et al 2012)

Groin irradiation in LN positive disease

The AGO-Care-1(2015, 2022)

- Adjuvant RT in node +ve results in less " Vulva only " recurrence
- The benefit of adjuvant radiation consistent regardless of the number of positive nodes, grade, or depth of invasion.
- Better DFS in HPV +ve compared to HPV neg tumors (2022)
- Despite adjuvant treatment poor outcome in node positive patients- **regardless of number of positive nodes-chemotherapy a possible option to improve prognosis**

NCDB analysis (2015)

- Unadjusted median survival without and with adjuvant chemotherapy was 29.7 months and 44.0 months. Weekly **Radiosensitizing chemotherapy, preferably with weekly cisplatin, is recommended**

Locally advanced Inoperable vulvar cancers

Def: Radical excision would require functional compromise or sacrifice of functionally important midline structures.

- Anorectal, urethral, or bladder involvement (in an effort to avoid colostomy and urostomy)
- Disease that is fixed to the bone
- Gross inguinal or femoral node involvement (regardless of whether a debulking lymphadenectomy was performed)

- **Neo-Adjuvant RT**
- **Definitive RT/ Chemo RT**
  - Improve Organ preservation
  - Reduce surgical treatment morbidity
  - Borrowed experience of radio sensitization effect in cervical and anal cancers

Evidence for Chemo Radiation in Vulvar Cancer

GOG-101, Moore et al,1998

N=71 Preoperative Split- course chemoRT (47.6Gy with 5-FU+Cisplatin)

48% Clinical CR ; 35% pathologic CR

GOG-205 Moore, et al, 2012

- Dose 57.6Gy; Omitted 5-FU ;**63.8% clinical CR ; 50% pathological CR**

NCD Database, Rao et al, 2015

- 74% Recd definitive chemoRT; Median **RT dose 59.4(40–79.2) Gy**
- **5 yr OS CRT vs RT (49.9% vs. 27.4%, p< 0.001)**

NCD Database, 2017

- Comparable survival with **RT doses >55 Gy + conc. chemo, with pre-op CRT + Surgery**

Principles of RT- Vulvar Cancers

Target Volume: Vulva, both groins and lower pelvic LN

Location and depth of inguinal LN V. Imp. Range (2cm- 18cm!)

Frog- Leg Position minimizes the bolus effect of skin folds

Bolus: for adequate dose to primary tumor particularly with high energy beams. Bolus over the groins -extracapsular extension of lymph nodes or skin involvement.

Thermo-luminescent dosimeters used early in treatment to confirm the intended dose is delivered

Vulva should be treated in node positive patients no local high-risk features

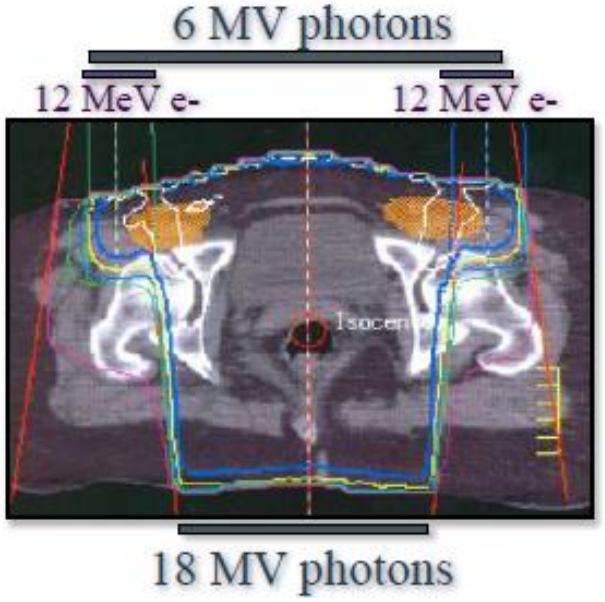
Interval between surgery and RT max.8-10 weeks

Total OTT of Radiotherapy <8 weeks

Adjuvant radiation following surgery <105 days (NCDB,2021)

Conventional radiation techniques

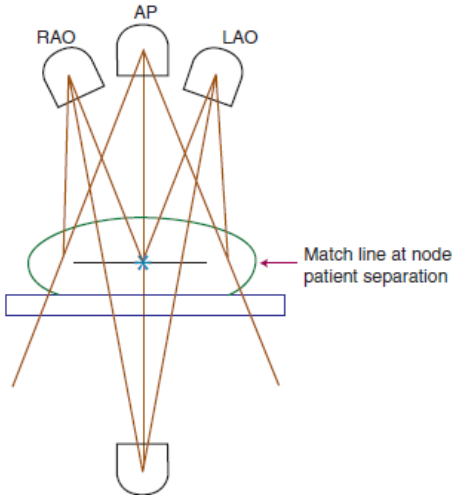
- Parallel opposed Anterior- posterior fields
- Wide AP- Pelvis+ Ing LN;Narrow (Photon electron field)
- Modified segmental boost technique



Photon-Electron field

Disadvantages:

- Poor conformity
- Electrons insufficient in obese cases
- Large areas treated
- Increase skin reactions
- Treatment breaks
- Limitation to deliver therapeutic doses



Modified segmental boost technique

IMRT

Advantages

- Improved conformity
- Dose escalation – better loco-regional control
- Elimination of match problems
- Reduced dose to OAR; reduced toxicity
- Ability to protect skin
- SIB possible

Disadvantages

- Steep learning curve
- IMRT has trouble optimizing targets that extend to the skin-air gaps

DRIVE Multicenter study (Rishi et al, 2022)

Median tumor dose 64 Gy (52-74.8 Gy)

83% received concurrent chemotherapy

Complete clinical response 81.3%

5 yr Local control 73% and 5 yr Overall survival 55%

Determinants of LC:

Stage III/ IV disease

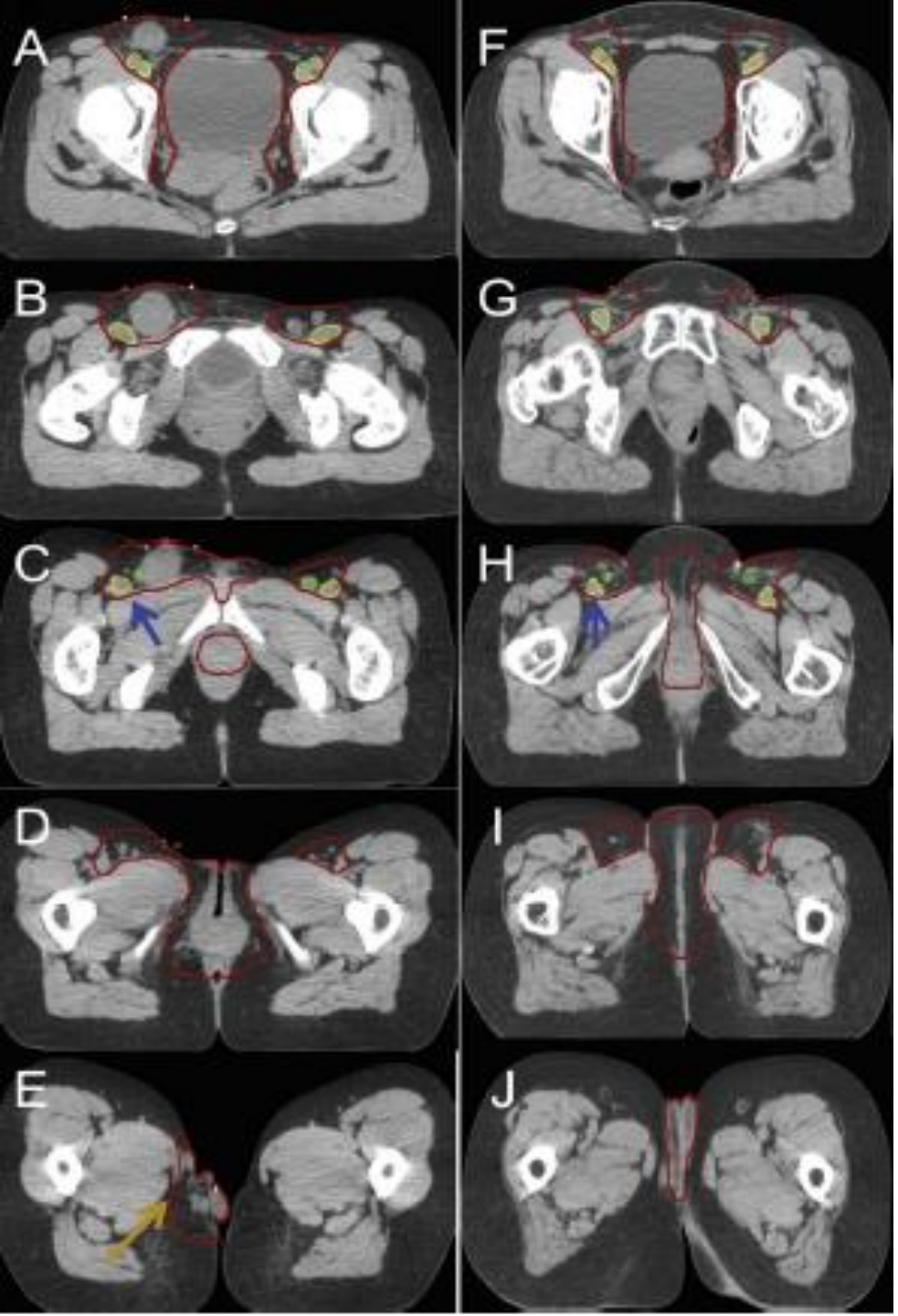
Non IMRT techniques

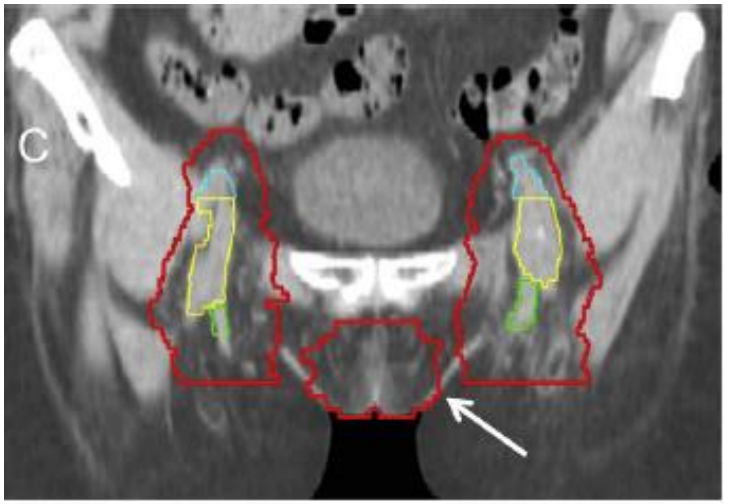
< 2 cycles chemo

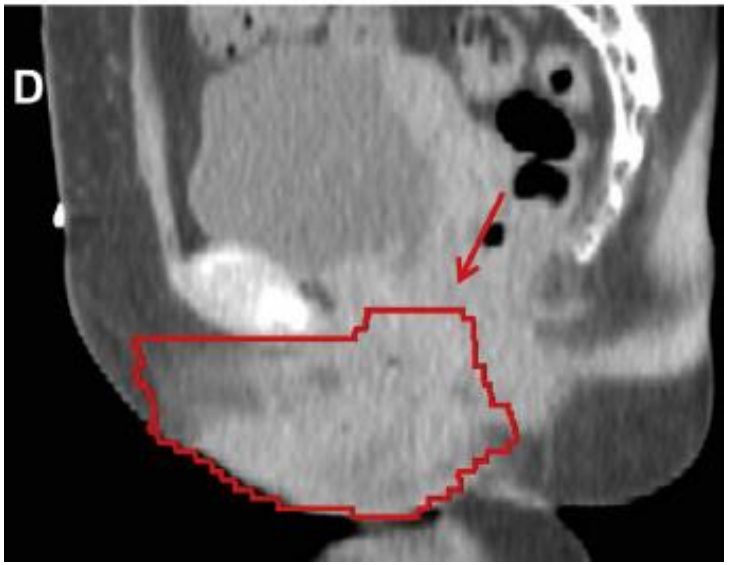
GOG 279 (SGO,2023)

- Weekly Gem 50 mg/m^2 and cisplatin 40 mg/m^2 weekly
- The IMRT dose to the vulva 64 Gy, doses to the groin according to lymph node status.
- The CCR rate 71.2%, Path CR 73.1%and 12 mths PFS 74%, 84% completed therapy
- Superior outcomes compared to GOG 205

Consensus Recommendations for Radiation Therapy Contouring and Treatment of Vulvar Carcinoma- Gaffney et al, IJROBP, 2015







Contouring –INGUINAL LN

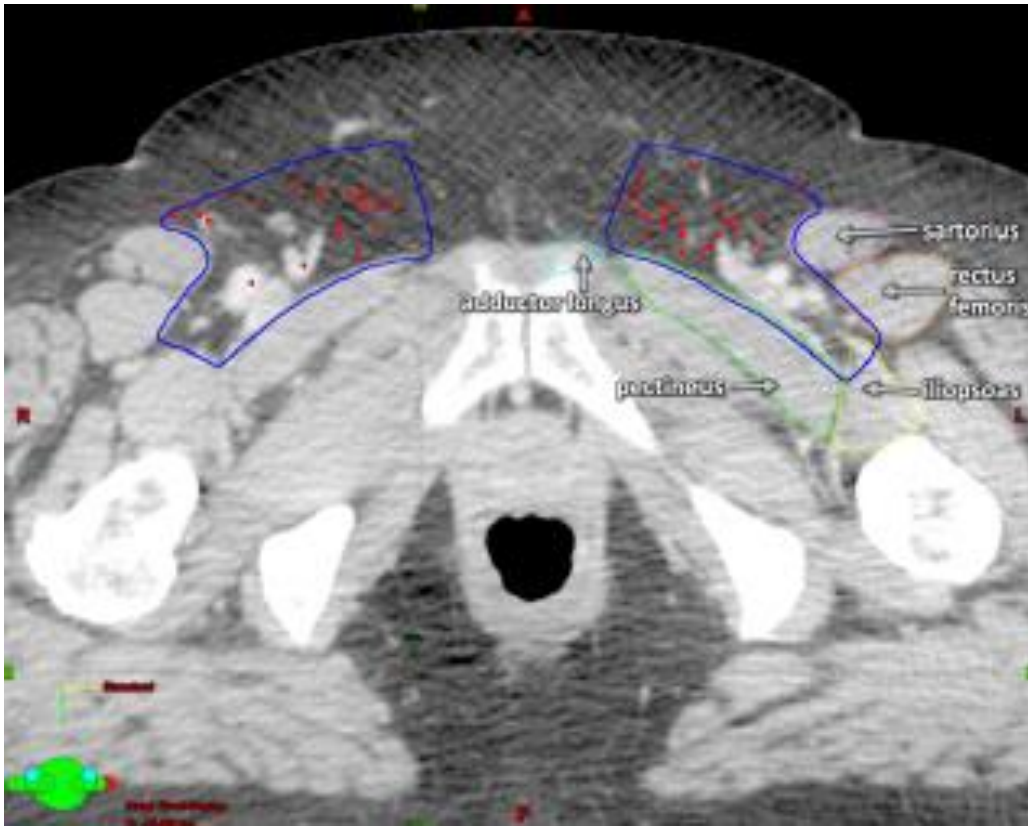
- Most of the inv. LN nodes ant, medial, or antero-med to Femoral vessels

- Caudal extent of ing region: 2 cm caudad to the saphenous-femoral junction. Transition btw Ing and ext iliac regions: caudad extent of the internal obturator vessels, appx level of upper edge of the superior pubic rami.

Boundaries

Lat: medial border of the iliopsoas
Med: lat border adductor longus or medial end of pectineus
Post: iliopsoas muscle laterally and ant aspect of pectineus medially
Ant: Ant edge of sartorius muscle

Kim et al, PRO, 2012



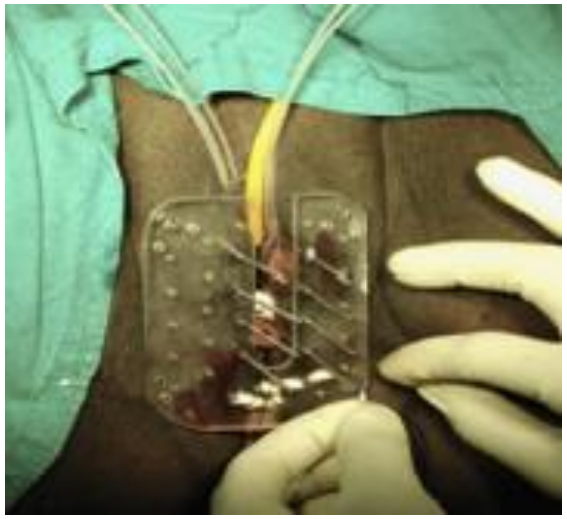
Brachytherapy

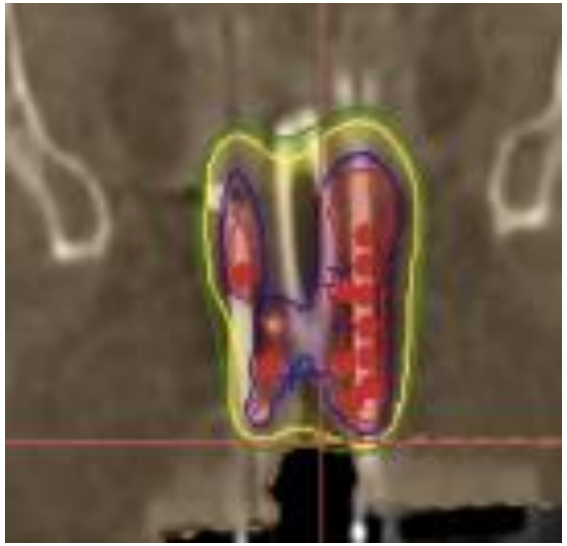
- As boost
- Salvage treatment in postoperative recurrent tumors

TMH,2017

30/38 patients – complete clinical response

5 yr Local control- 77%





Radiation dose in vulva cancer treatment

Primary surgical bed (post op, negative margins)- **45-50Gy**

Primary Surgical bed (post op, close or positive margin)- **54-60Gy**

Gross primary vulvar disease- **60-70Gy**

Clinically and or Radiological negative inguinofemoral LN- **45-50Gy**

Positive inguinofemoral LN, No ECE or gross residual ds- **50—55 Gy**

Positive inguinofemoral LN, ECE present- **54-60Gy**

Inguinofemoral LN (gross disease or unresectable)- **60—70 Gy**

Vaginal Cancer

Rare, representing only 10% of all vaginal malignant neoplasms and 1–2% of all gynecological cancers

Definition of primary vaginal cancer
Excludes any involvement of the cervix and/or vulva as well as any malignant lesion arising in the vagina within 5 years after the treatment of cervical cancer.

FIGO staging

Stage I: The tumor in the vagina. Not spread through vaginal wall

Stage II: The tumor spread through the vaginal wall but not to the walls of the pelvis.

Stage III: Cancer has spread to the lymph nodes in the pelvis.
Cancer has spread to the pelvic wall

Stage IVA: Spread to the bladder, rectum, or beyond the pelvis. The lymph nodes may or may not be involved.

Stage IVB: Distant Metastasis

Treatment of Vaginal Cancer

Surgery- Vaginectomy, Radical Hysterectomy

- Limited role due to the proximity bladder, rectum, and urethra.
- May be considered in stage I tumors (<2 cm dia. limited to the proximal vagina)
- Reported equal survival rates with surgery and radiotherapy In Stage I &I I ; 55% received post op radiotherapy (Yang et al,2020)
- Pelvic exenteration
  - Stage IV disease with recto-vaginal or vesico-vagina fistula
  - Central recurrence post RT

Role of Radiotherapy

EBRT + Brachytherapy

Treatment of choice – esp in locally advanced tumors

Advantage- Preservation of vagina and other OAR's

Reduce the volume of the primary vaginal tumor, provide regional lymph node control, and eradicate other microscopic disease.

IMRT preferred, Pre treatment MRI for better assessment of disease

Concurrent chemoradiotherapy-an independent prognostic factor for better 5 yr overall survival (56 mths Vs 41 mths) NCDB database

Brachytherapy-Essential component in Mx of Vaginal cancer

Longer Median 2 yr OS with use of brachytherapy in vag cancer (6.1 yrs Vs 3.6 yrs) – SEER analysis-2016

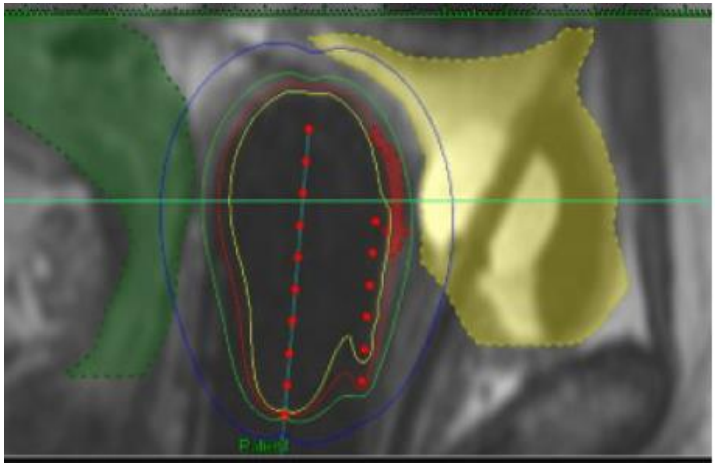
Brachy techniques

Techniques vary depending on the **tumor's response and site of the disease**.
Superficial tumors (<5–7 mm dia)- ICA

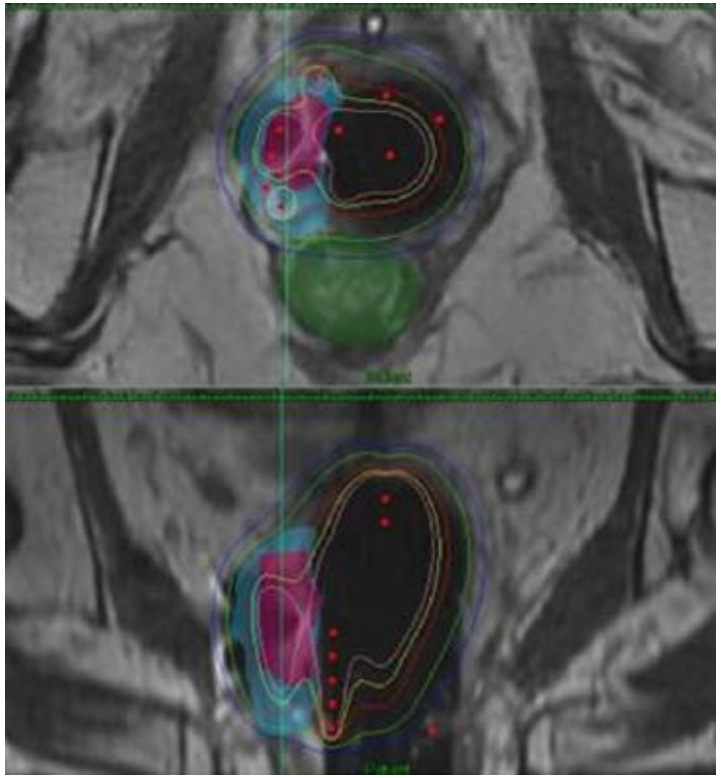
Very superficial Lesions- normal cylinder/ multi-channel cylinder (better coverage and depth dose)

Tumors thicker >7mm dia- combination applicator (cylinder and needles.) free-hand or with a perineal template.

IGABT (Gec- Estro)- Median Dose 79 Gy local control 82–93%; 2 yr OS 62–91%. Reduced severe toxicity ranging (Westerveld, 2020)



Multi-channel Cylinder



Cylinder & Needles

IGABT (Gec- Estro)- Median Dose 79 Gy local control 82–93%; 2 yr OS 62–91%. Reduced severe toxicity ranging (Westerveld, 2020)

EBRT Boost

In very large tumors or unfavorable anatomy for brachytherapy
Dose of 66 to 70 Gy using conformal techniques
5yr Local control 76%, Disease free survival 67% (Frank et al, 20
5 year and 10 year cumulative rate of major complications
10% and 17%,

Conclusion

VULVAR CANCER

•Adjuvant treatment is recommended when surgical margins of the primary are <8 mm or when positive lymph nodes are identified.

•IMRT should be preferred, allows dose escalation without treatment interruptions may reduce both acute and chronic toxicity.

•Concurrent chemotherapy represents the standard of care in advanced disease

VAGINAL CANCER

- Rare cancer- diagnosis is by exclusion
- Surgery has a limited role in early stages
- Concurrent chemoradiation with brachytherapy represents the standard of care


PGIMER
स्नातकोत्तर चिकित्सा शिक्षा एवं
अनुसंधान संस्थान - चण्डीगढ़

Adverse effects after treatment

Acute

- The most significant is the skin reaction in the vulva–perineal region and inguinal folds
- Moist desquamation by the 3rd–5th weeks of treatment is common; a treatment break is usually necessary
- Diarrhea and cystitis are other common acute side effects
- Acute hematologic toxicity is common and depends on the type and intensity of the chemotherapy used

Late

- Common late toxicities include telangiectasia, atrophy of skin, fibrosis, dryness, and shortening/narrowing of the vagina
- Avascular necrosis of the femoral head has been reported
- Femoral neck fracture is associated with osteoporosis and smoking
- Groin radiation can cause lymphocyst formation, lymphedema, and infection

Other

- Significant psychosexual consequences relating to sexual function and body image may occur