Non-squamous carcinoma: vulvar and vagina

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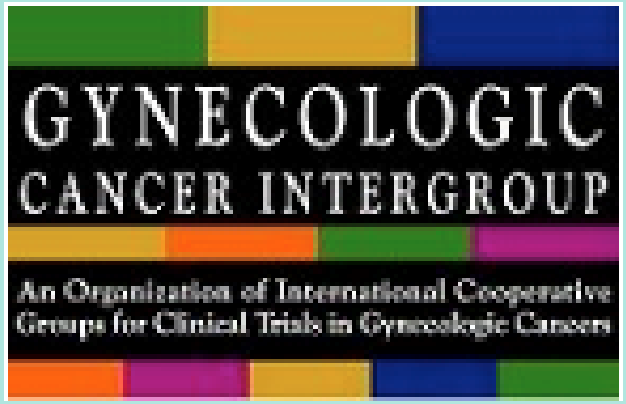

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Rare variants of rare diseases

Lifetime risk for vulvar cancer: 0.3%
20% non-squamous subtypes

Vagina: WHO classification 2014

Adenocarcinomas

- Endometrioid carcinoma
- Clear cell carcinoma
- Mucinous carcinoma
- Mesonephric carcinoma

Other epithelial tumors

- Adenosquamous carcinoma
- Adenoid basal carcinoma

High-grade neuroendocrine carcinoma (NEC)

- Small / Large cell NEC

Mesenchymal malignant tumors

- Leiomyosarcoma
- Rhabdomyosarcoma (Embryonal, alveolar, pleomorphic)
- Undifferentiated sarcoma
- Other sarcomas (Ewing sarcoma / PNET, alveolar soft part sarcoma, angiosarcoma, malignant peripheral nerve sheath tumor (MPNST), synovial sarcoma)

Mixed epithelial and mesenchymal tumors

- Adenosarcoma
- Carcinosarcoma

Germ cell tumors (Yolk sac tumor)

Malignant melanoma

Secondary tumors

Vulva: WHO classification 2014

Glandular tumors

- Paget disease
- Tumors arising from Bartholin and other specialized anogenital glands
  - Bartholin gland carcinoma
  - Adenocarcinoma of mammary gland type
  - Adenocarcinoma of Skene's gland origin
  - Phylloides tumor (malignant)
- Adenocarcinoma of other types
  - Sweat gland type or intestinal type

High-grade neuroendocrine carcinoma (NEC)

- Small / Large NEC / Merkel cell tumor

Mesenchymal malignant tumors

- Leiomyosarcoma
- Rhabdomyosarcoma (embryonal, alveolar)
- Ewing sarcoma / PNET
- Epithelioid sarcoma
- Alveolar soft part sarcoma
- Other sarcomas (liposarcoma, angiosarcoma, malignant peripheral nerve sheath tumor (MPNST), synovial sarcoma, Kaposi sarcoma, fibrosarcoma, dermatofibrosarcoma protuberans)

Germ cell tumors (Yolk sac tumor)

Malignant Melanoma

Secondary tumors

Melanoma: Initial work-up

- **Melanoma vulva/vagina = mucosal melanoma (not cutaneous melanoma)**
- **Best staging system is unclear: FIGO, AJCC, Ballantyne**
- **Initial biopsy to confirm diagnosis**
  - Key pathologic features needed
    - Tumor thickness (most important); Presence of ulceration; Mitosis/mm^2; LVSI; TILs
- **CT chest/abdomen (PET/CT also acceptable based on local practice) and MRI brain to rule out metastases**
- **MRI pelvis**
  - For all vaginal melanomas
  - For larger vulvar melanomas that may require larger resections
- **Genomic testing (including IHC)**
  - BRAF, c-Kit, NRAS (standard minimum). NTRK1-3, ALK, and ROS
  - Consider broader genomic profiling if possible

Melanoma vulva: Staging

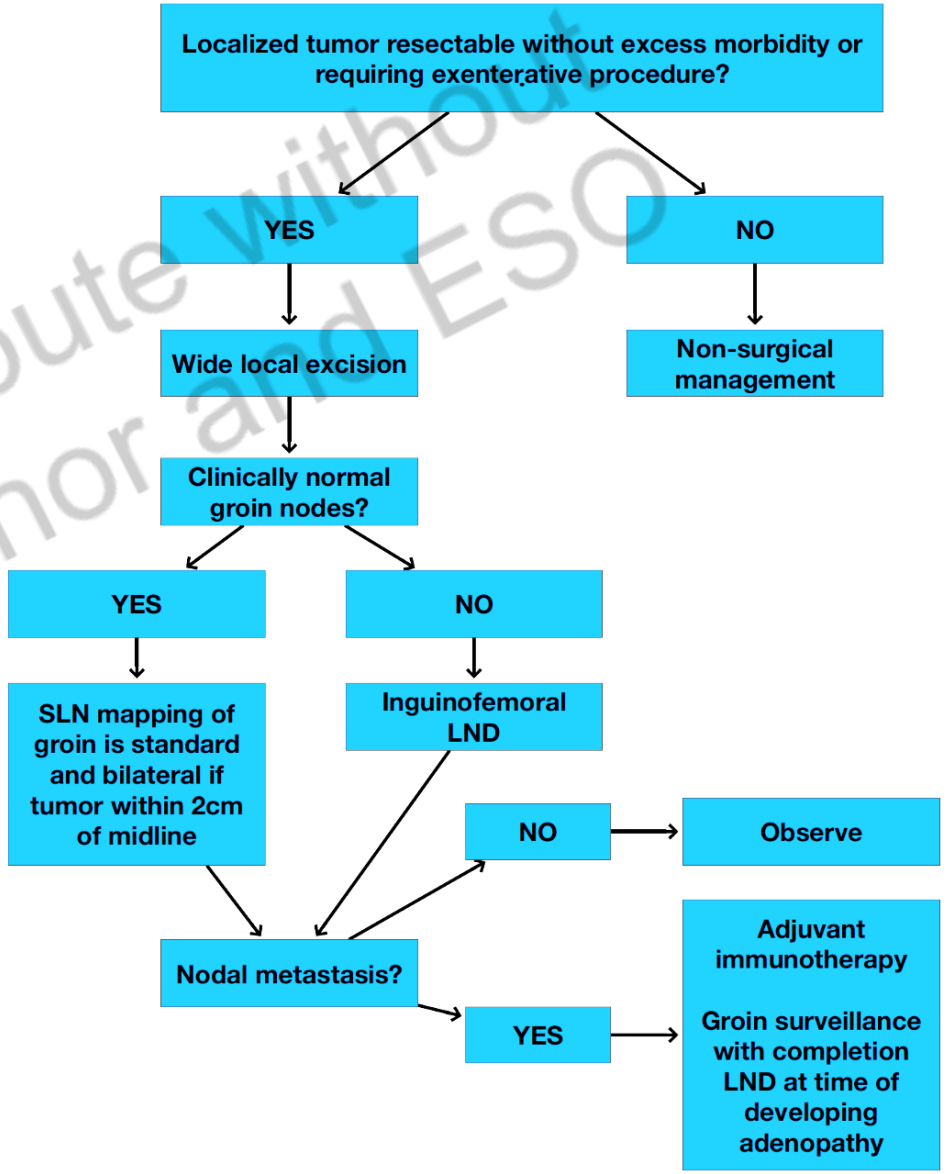
STAGE	FIGO (Not melanoma specific)	STAGE	AJCC (pathologic TNM melanoma staging)
I IA IB	Confined to vulva/perineum AND (-) groin nodes <=2cm tumor AND stromal invasion <=1mm >2cm tumor OR stromal invasion >1mm	I IA IB	No nodal or distant mets Thickness <=1mm with or without ulceration Thickness 1.01-2.0 mm without ulceration
II	Any size tumor with extension to adjacent strutcures (1/3 lower vagina, 1/3 lower urethra, and/or extension to anus) AND (-) groin nodes	II IIA IIB IIC	No nodal or distant mets Thickness 1.01-2.0 mm with ulceration or 2.01-4.0 mm without ulceration Thickness 2.01-4.0 mm with ulceration or >4 mm without ulceration Thickness >4mm with ulceration
III IIIA IIIB IIIC	Tumor any size and local extension AND (+) groin nodes sub (i) 1 LN (>=5mm met); sub (ii) 1-2 LN (<5mm mets) sub (1) >=2 LN (>=5mm met); sub (ii) >=3 LN (<5mm met) Extracapsular nodal extension	III IIIA IIIB IIIC	Regional nodal metastasis but no other distant metastases Any thickness without ulceration and 1-3 micrometastic LNs Not IIIA or IIIC Any thickness with ulceration AND any macrometastatic LN or intransit mets/satellites without nodal mets Any thickness +/-ulceration with >=4 LN mets (any type), matted nodes, or in transit/satellites and metastatic nodes
IV IVA IVB	Tumor invades other regional structures or distant mets sub (i) upper urethra and/or vaginal mucosa, bladder mucosa, rectal mucosa or fixed to bony pelvis; sub (ii) fixed or ulcerated groin nodes Any distant mets including pelvic lymph nodes	IV	Any metastatic disease including non-regional (i.e. pelvic) node mets, any visceral mets (i.e. bladder/rectal mucosa)
			“Macrometastatic” LN mets defined as nodes that are clinically detectable or when have extracapsular extension

Melanoma vulva/vagina: Staging

- **Simplified staging system originally intended for H&N melanomas but can be applied to all mucosal melanomas**
  - **Stage I – clinically localized disease**
  - **Stage II – regional nodal disease**
  - **Stage III – distant metastatic involvement**

Melanoma: primary treatment

- **Wide Local Excision**
  - Clinical margins to obtain:
    - 1cm for tumor thickness <=2mm
    - 2cm for tumor thickness >2mm
  - If positive resection margin:
    - Consider re-resection
    - If re-resection not possible, options to consider are imiquimod 5%, hypofractionated RT, or close observation
- **SLN positive cases**
  - Completion inguinofemoral LND unnecessary
  - Adjuvant CPI therapy w PD-1/PD-L1 inhibitor (other if BRAF mutant)
  - Groin surveillance every 3 months for first 3 years:
    - Groin US alone or alternating groin US with CT C/A/P
  - Completion inguinofemoral LND for evolving adenopathy
- **For grossly suspicious groin nodes, unclear if complete LND needed or just resection of enlarged nodes**
- **Locally advanced tumors requiring an extensive resection**
  - Immunotherapy alone if metastatic disease
  - Immunotherapy and hypofractionated RT if localized (including groin mets)
  - Exenterative procedures only reserved for highly selected cases



Melanoma vulva/vagina: initial therapy

- **Consider clinical trials if available**
- **Adjuvant immunotherapy options (BRAF V600E/V600K wildtype or unknown)**
  - Single agent preferable
  - Pembrolizumab 200 mg IV q3 weeks for total 18 doses
  - Nivolumab 3mg/kg IV q2 weeks x4 then q12 weeks for up to 1 year
  - Ipilimumab 10mg/kg IV q3weeks x4 then q12 weeks x4
- **Adjuvant therapy for V600E/V600K mutations**
  - Dabrafenib 150mg po BID + trametinib 2mg po QD
- **Hypofractionated radiation therapy for locally advanced newly diagnosed**
  - 600 cGy x6 delivered every other day
  - Target volume = gross disease +0.5-1cm
  - Concurrent single agent immunotherapy
  - Consideration of surgical resection depending on response and continued absence of distant disease

Melanoma vulva/vagina: recurrence

- **Highly individualized → clinical trial if available, genomic profiling**
- **Most therapy should be extrapolated from current standard therapies for cutaneous melanoma**
  - **Isolated and resectable**
    - Complete resection → Exenterative procedures in highly selected situations
    - Consider adjuvant immunotherapy
  - **Isolated but not resectable**
    - Consider hypofractionated RT if not received before
    - Re-irradiation may be consideration if hypofractionated RT before
    - Concurrent immunotherapy
  - **Not isolated metastatic recurrence**
    - Use standard management options for cutaneous melanoma

Adenocarcinoma: vulva and vagina

- **FIGO is the staging system**
- **Important factors to consider**
  - Vagina: Clear cell carcinoma (Endometrioid carcinoma) historically associated with use of diethylstilbestrol (predominately 15-30 years)
  - Vagina: Mesonephric adenocarcinoma
  - Vulva: Majority of Adenocarcinoma derive from Bartholin gland, minority sweat glands including Skene gland (prostate specific antigen positive)
  - FIGO stage, size of the tumor, histology are prognostic factors
- **Risk of relapse is mainly related to tumor stage**

Adenocarcinoma: primary treatment

- **Surgical procedures for vulva tumors include**
  - Local wide excision
  - Vulvectomy
  - In case of positive margins further resection or – if not feasible- radiotherapy
  - Inguinofemoral lymph node dissection
  - Sentinel lymph node dissection
- **Surgical procedures for vaginal tumors include**
  - Vulvectomy with vaginal resection
  - Radical hysterectomy with vaginal resection
  - No surgical lymph node staging (CT/MRI/PET)

Adenocarcinoma: systemic treatment and recurrence

- **Adjuvant therapy**
  - In node positive patients radiotherapy
- **Alternative therapy**
  - For vaginal carcinoma primary radiotherapy w/o chemotherapy
- **Therapy or recurrent disease**
  - For vaginal carcinoma primary radiotherapy w/o chemotherapy
  - For vulvar carcinoma consider further surgery, if not feasible radio(chemo)
  - Consider PDL-1 testing for immunotherapy

Bartholin gland carcinoma

- **FIGO is the staging system**
- **Important factors to consider**
  - Bartholin gland carcinoma approximately 30-50% are of squamous histology and are thought to originate in the Bartholin duct, and the remaining 50-70% include adenocarcinoma and adenoid cystic carcinoma, which mimics behavior of salivary gland carcinoma of the same histology
  - Lesions are deep within the vulva and often misdiagnosed as a Bartholin gland abscess or cyst
  - FIGO stage, size of the tumor, histology are prognostic factors
- **Risk of relapse is 20-40%**

Bartholin gland carcinoma: treatment

- **Surgical procedures include**
  - Local wide excision
  - Vulvectomy +/- flaps
  - In case of positive margins further resection or – if not feasible- radiotherapy
  - (Unilateral) Inguinofemoral lymph node dissection
  - Sentinel lymph node dissection
  - For large tumors consider neoadjuvant chemotherapy (cisplatin and 5-fluorouracil)
- **Adjuvant therapy**
  - In node positive patients radio(chemo)therapy
- **Alternative therapy**
  - Primary radiotherapy w/o chemotherapy
- **Therapy for recurrent disease**
  - Surgery if feasible
  - Radiotherapy
  - Chemotherapy

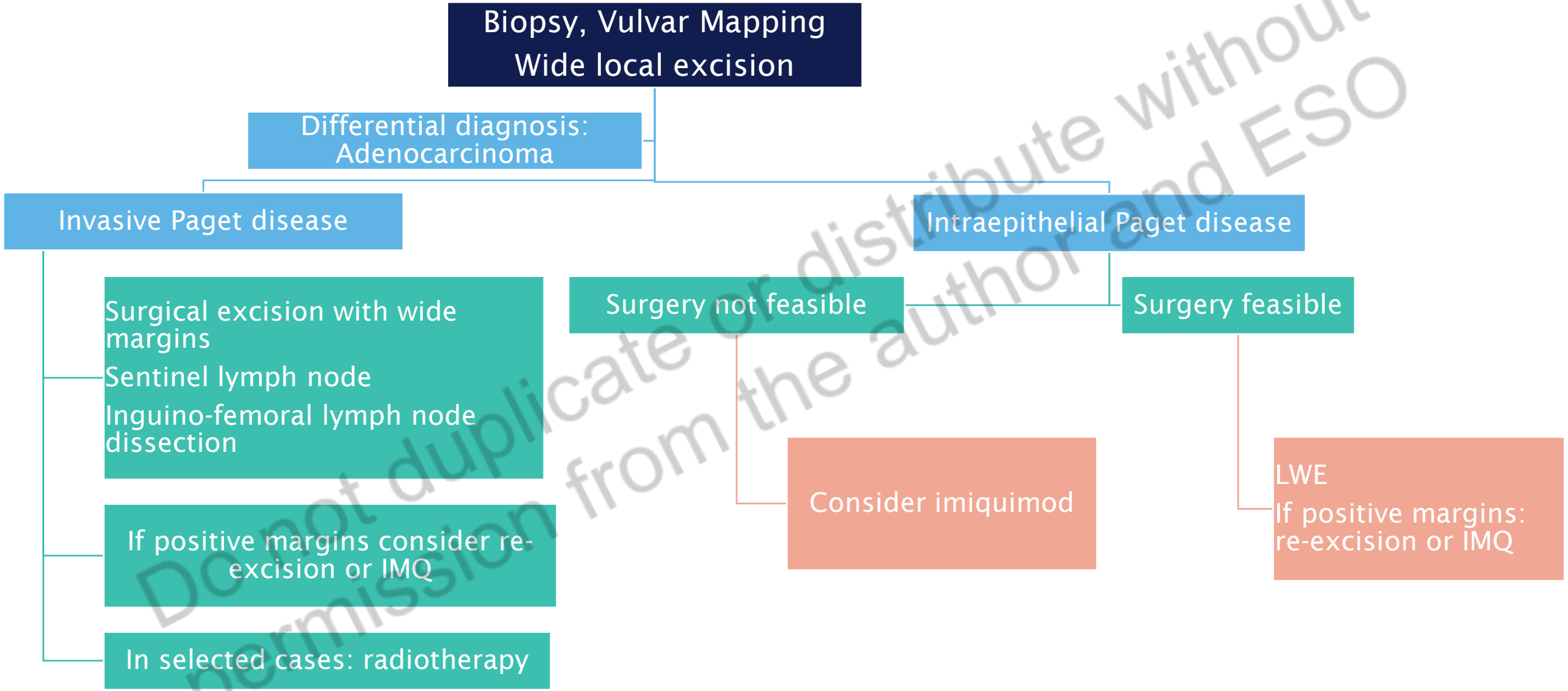
Paget disease

- **The initial diagnosis includes**
  - Physical exam incl. rectovaginal examination and symptoms
  - Cystoscopy and proctoscopy
  - Pelvic ultrasound or MRI and CT scan including abdomen and chest for advanced stage (exclude secondary tumors)
  - Biopsy for large lesions or excision for smaller lesions, consider vulva mapping
- **Important factors to consider**
  - Association with underlying malignancies e.g anorectal carcinoma or urothelial carcinoma
  - Exclude breast or gastrointestinal tumors
  - Invasive vs. intraepithelial Paget disease
  - Tumor Size and FIGO stage
  - Negative margin status does not preclude recurrences
- **Risk of relapse is 30%, median time to relapse 3 years**
- **Disease related mortality is <10%**

Paget disease: treatment

- **Surgical procedures include**
  - Local wide excision with free margins
  - Vulvectomy
  - Mohs surgery
  - Inguinofemoral lymph node dissection
  - Sentinel lymph node dissection
- **Adjuvant therapy**
  - In node positive patients radiotherapy
- **Alternative primary therapy**
  - Topical therapy with imiquimod (self-applied cream) for intraepithelial disease
  - Radiotherapy
  - In case of FIGO stage IV consider metastasis of undetected underlying malignancy (biopsy). Cisplatin, fluorouracil and bleomycin are options.
  - Photodynamic therapy, and laser therapy have also been proposed

Paget disease: work flow



Follow-up: non-squamous vulva/vaginal carcinoma

- **Follow-up is dependent on primary tumor**
- **Paget disease**
  - Local inspection (consider vulvoscopy)
  - Re-biopsy to confirm recurrence
  - CT/MRI in case of advanced disease only (node negative vs node positive cases!)
- **Adenocarcinoma**
  - Local inspection (consider vulvoscopy)
  - Ultrasound for nodal recurrences
  - CT/MRI or PET for distant recurrences
  - Re-biopsy to confirm recurrence
- **Melanoma**
  - Local inspection (consider vulvoscopy)
  - Groin surveillance every 3 months for first 3 years in node positive patients
  - CT chest/abdomen/pelvis and MRI brain (CT if MRI not feasible) to rule out metastases

- **Frequency**
  - 3-6 monthly for 5 years

Take home

- Extremely rare malignancies
- Melanoma = mucosal melanoma
- Bartholin gland cancer often misdiagnosed as abscess/cyst
- Paget disease: invasive vs intraepithelial
  - Topical IMQ next to surgery