Genital Skin Cancer

A Practical Review for Mohs Micrographic Surgeons

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ACMS

Relevant Financial Relationship Disclosure Statements

Maral K. Skelsey, MD

I will not discuss off label use and/or investigational use of any drugs or devices.

I have no relevant financial relationship(s) related to my role in this session to disclose.

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Genital Skin Cancer Overview

Rare, but often extensive; can be aggressive

Delay in Diagnosis & Treatment

- Stigma assoc. w/ genital lesions
- Common misdiagnoses: eczema, tinea, STI, benign melanosis, contact dermatitis

Genital Skin Cancer Overview

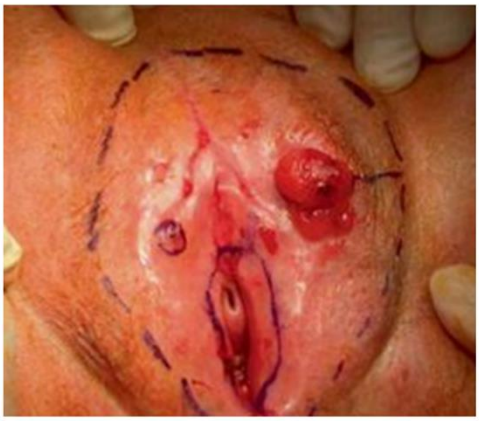
I Vulvar Carcinoma
II Penile Carcinoma
III Anorectal Carcinoma
IV Extramammary Paget's Disease
V Malignant Melanoma

Vulvar Carcinoma

Squamous Cell Carcinoma (SCC)
- Vulvar cancer is typically SCC

HPV(+)
- 20% of all invasive SCC
- Younger women
- HPV16 (72%); p16(+) hallmark of HPV(+) SCCs
- 76% of SCC are warty or basaloid

HPV(-)
- 80% of inv. vulvar SCC
- Older women
- LS (+)
- **2-5% of vulvar LS progress to SCC**



(van de Nieuwenhof 2011)(Herr 2014)(Gross 2004)(Brown 1988)(Ferrandiz-Pulido 2012)

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Vulvar SCC 4% of female genital malignancy (Herr)
Type 16 + 18 (+ 31, 33, 35, 39, 45, 51, 52, 54, 56, 58, 59, 66, 68, 69) HPV associated with oncogenesis
HPV DNA found in 50% of vulvar carcinoma
*Could not find "Perunovic 2007"

Vulvar Carcinoma

4th most common gynecologic malignancy in US (after uterine, ovarian, and cervical)

- Skin-colored plaque, ulcer or nodule on labia majora, minora, perineum, clitoris, or mons
- Most asymptomatic, some pruritus or bleeding
- 5% Multifocal; All vulvar, perianal skin should be examined
- 90% vulvar tumors are SCC
- 22% 2nd malignancy - cervical ca most common
- Complete pelvic exam and colposcopy

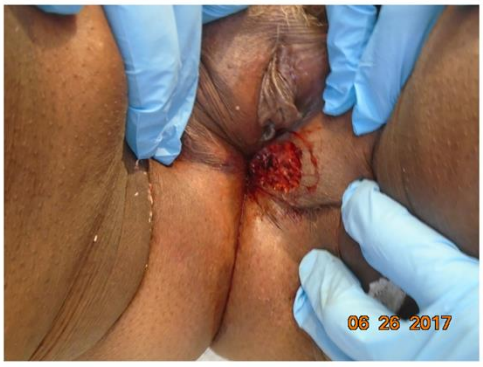
Multifocal vulvar SCC pre-op

(Duong et al. 2007)

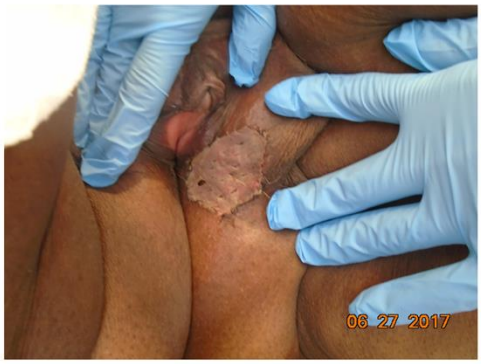
Need clinical photo of vulvar scc and lichen sclerosus- side by side

Vulvar Carcinoma

Left labia minora 72 y/o F



Mohs defect



Full-thickness skin graft

Vulvar Carcinoma

- Multiple scouting biopsies may be necessary
- HPV testing on specimen and colposcopy
- 30% of patients have lymph node involvement
- LN involvement assoc. with tumor thickness, stromal invasion, capillary-lymphatic space invasion

(van de Nieuwenhof 2011)(Herr 2014)(Gross 2004)(Brown 2018)(Ferrandiz-Pulido 2012)

HPV(+/-) Precursor Lesions

HPV(+)

- High-grade squamous intraepithelial lesion
- (HSIL) 6.5% progress to SCC
- 1% regress w/o tx
- 9-16% HSIL progress to invasive disease (studies small)

HPV(-)

- Differentiated VIN (dVIN)
- Higher progression to SCC rate than HSIL (usual VIN)
- Often associated with LS
- 1-3% of women with LS develop SCC
- LS present in 50% of women w/ SCC
- **>50% HPV(-) SCC have adjacent dVIN**

(Garland 2018)(Jones 1995)(van de Nieuwenhof 2011)(Herr 2014)(Gross 2004)(Brown 1988)(Ferrandiz-Pulido 2012)

(Garland 2018) + (Jones 1995) claim **87.% of untreated HSIL progress to cancer

HPV(+/-) Precursor Lesions

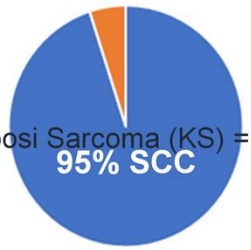
Treatment recommended for all Pts:

- MMS, WLE, CO2 last, Imiquimod, 5FU, PDT
- Surgery w/ margin 0.5-1.0cm conserving clitoris, urethra anus, or other critical structures
- Ablative laser therapy w/ margin 0.5-1cm of normal skin (0.2cm deep)
- If hair bearing need to treat to base of follicles (down to subcutis)
- Imiquimod 5% x3/wk fo 12-20 wks, unresponsive lesions are excised,
- Close clinical follow-up post-tx
- 81% had complete or partial response

(Garland 2018)(Jones 1995)(van de Nieuwenhof 2011)(Herr 2014)(Gross 2004)(Brown 1988)(Ferrandiz-Pulido 2012)

Penile Carcinoma:

- Overall incidence < 1.00/100,000 males EU/ USA
- 2,030 cases/ yr; 340 deaths/ yr (2016 estimate)
- 1-2% of malignant diseases in men outside USA
- Peak age (60-69 y/o); increases with age (50-70 y/o)
- **SCC > 95% penile malignancies**
- BCC + MM + Extramammary Paget's Disease (EMPD) + Kaposi Sarcoma (KS) = 5%

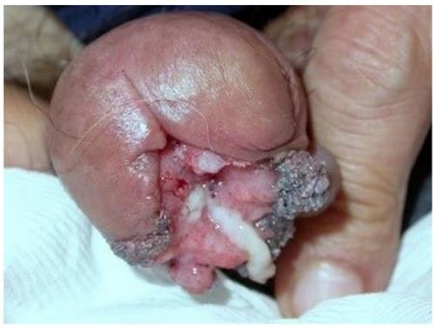


(Necchi 2017)(Backes 2009)(Chaux 2013)(Castellsague 2002)(Barnholtz-Sloan 2007)(Siegel 2014)

Penile SCC

- **15-60% patients postpone presentation 1-yr**
- **66% w/ localised disease only**
- **Distant mets (1-10%)**
- **DDX:**
  Condyloma, syphilis, chancroid, psoriasis, LP

Structure	Frequency
Glans	48%
Prepuce	21%
Glans + Prepuce	15%
Coronal Sulcus	6%
Shaft	<2%



Verrucous carcinoma of the meatal orifice + ventral glans penis

(van de Nieuwenhof 2011)(Herr 2014)(Gross 2004)(Brown 1988)(Ferrandiz-Pulido 2012) (Siegel 2014)(Hernandez 2008)(Ornellas 2008) (Marchionne 2017)

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Penile SCC occurs almost exclusively in uncircumcised men. ... **Penile SCC** most commonly presents between the ages of 50 and 70 years. [3]. The majority of lesions are found on the **glans** (48%), followed by the **prepuce** (21%), both **glans** and**prepuce** (15%), coronal **sulcus** (6%), and **shaft** (<2%).

Penile Carcinoma

Modified from Table 1 (Hakenberg 2017)

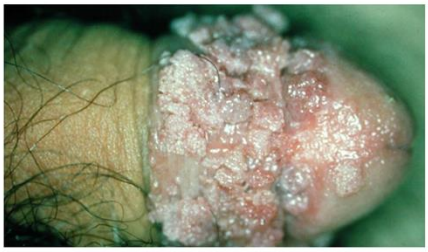
Risk Factor	Relevance
Phimosis	Odds ratio (OR) 11-16 vs. no phimosis
PUVA	Incidence rate ratio 9.51 w/ >250 tx
Smoking	5x increased risk vs. non-smokers
Multiple sexual partners; early age sexual intercourse	3-5x increased risk
HPV (+)/ condylomata acuminata	22.4% in verrucous SCC; 36-66.3% in basaloid-warty
Low SES; rural residence; marital status (unmarried)	Increased risk
Chronic penile inflam / Balanitis xerotica obliterans (LS)	Increased risk
Uncircumcised penis	Majority of cases

Phimosis (inability to retract foreskin) assoc. w/ chronic infection
Routine neonatal circumcision = lower incidence of penile cancer- but not CIS-
(Israeli Jews lowest incidence 0.3/100,000)

Penile Carcinoma

Human Papillomavirus

- HPV DNA found 30-40% invasive penile cancers
- HPV16 (72%)
- 5-yr survival rate (93%) HPV(+) vs. (78%) HPV(-)
- Others report no difference in 10-yr surv. rate



Condyloma acuminata of the penis, HPV(+)

(Hakenberg 2017)(Munoz 2006)(Nordenvall 2006)(Lont 2006)

Penile SCC

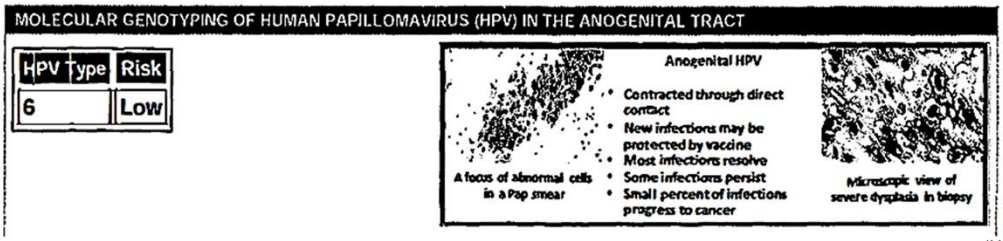
Modified from Table 3 (Hakenberg 2017)

Subtype	Frequency	Prognosis	HPV (+/-)
SCC (Common)	48-65%	Depends on location, stage, grade	HPV(-)
Verrucous carcinoma	3-8%	Good, no mets	HPV(-)
Sarcomatoid carcinoma	1-3%	Very poor, early vascular mets	HPV(-)
Papillary carcinoma	5-15%	Good, rare mets	HPV(-)
Warty-basaloid carcinoma	9-14%	Poor, high mets	HPV(+) (82%)
Mixed carcinoma	9-10%	Variable	HPV(+)
Warty carcinoma	7-10%	Good, rare mets	HPV(+) (39%)
Basaloid carcinoma	4-10%	Poor, frequent early inguinal nodal mets	HPV(+) (76%)

Penile SCC

Pathology Report should include:

- **Histological type of SCC**
- Grade
- Perineural invasion
- Depth of invasion
- Vascular invasion (venous/lymphatic)
- Irregular growth and front of invasion
- Urethral invasion,
- Invasion of corpus spongiosum / cavernosum
- Surgical margins
- **p16/HPV status**



(Hakenberg 2017)

Penile SCC Local Treatments

Treatment	Complications	Local Recurrence	Nodal Recurrence	Cancer-specific Deaths
Nd:YAG laser	None reported	10-48%	21%	2-9%
CO2 laser	Bleeding, meatal stenosis (both <1%)	14-23%	2-4%	None reported
Lasers (unspec.)	Bleeding (8%), local infection (2%)	11-26%	2%	2-3%
MMS	Local infection (3%), meatal stenosis (6%)	32%	8%	3-4%
Glans resurfacing	None reported	4-6%	Not reported	None reported
Glansectomy	None reported	8%	9%	None reported
Partial Penectomy	None reported	4-13%	14-19%	11-27%
Brachytherapy	Meatal stenosis (>40%)	10-30%	Not reported	None reported
Radiotherapy	Urethral stenosis (20-35%), glans necrosis (10-20%)	None reported	Not reported	None reported

Modified from Table 3 (Hakenberg 2017)

10-20 % of all malignancies

(Uronis 2007)

Perianal SCC

- Pain, bleeding; 20% asymptomatic
- Dx delayed as sx attributed to benign conditions such as hemorrhoids 70 = 80%
- In 2016, 8,200 new cases; incidence increasing
- 1.7 : 1 :: women : men
- 1,100 died of anal SCC; 1.4 : 1 :: women : men
- 50% present with node (-) disease
- 1/3 nodal disease
- 10-15% distant met

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Reference:The American Society of Colon and Rectal Surgeons
Clinical Practice Guidelines for Anal Squamous Cell
Cancers (Revised 2018)

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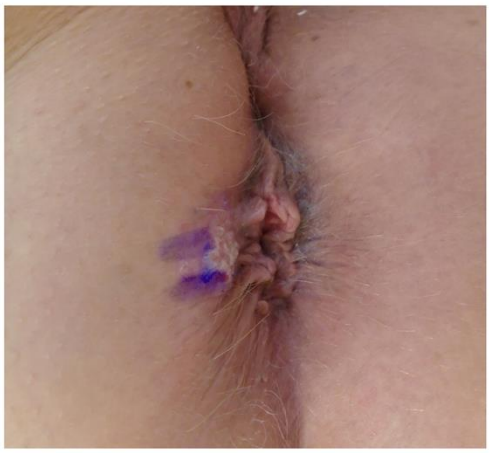
Squamous cell cancers of the anal canal and perianal region remain one of the least common malignancies arising from the alimentary tract. As of 2016, it is estimated that 8200 new cases of squamous cell cancers of the anus were diagnosed in the United States, with 1.7 times as many women as men affected.1 Within this same time period, ≈1100 patients were estimated to have died of anal cancer, with cancer deaths among women being 1.4 times the number observed among men. Although squamous

cancers of the anus remain relatively rare GI malignancies,
2 factors have nonetheless focused greater attention

SCC in situ

Right anus, 56 y/o F

- Lesion of the right anus
- 6 mo h/o pruritic plaque tx'd steroid & anti-fungal
- s/p hemorrhoidectomy 1 yr prior
- Biopsy: SCC in situ (HPV+) Ber-EP4, CK7 – (r/o EMPD)



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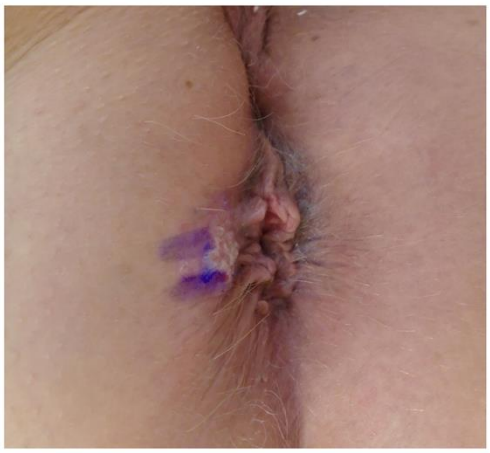
Hx 56y/o woman w/ 1-yr Hx of intermittent pruritus ani
Tx with topical steroid and topical antifungal
1-yr Hx of HPV treated with podophyllin
1yr prior status post hemorrhoidectomy surgery
Presented w/ 2cm macerated plaque
Condyloma b/w vaginal introitus and anus
Bx revealed SCC in situ, ber EP4 + ck7 (-) for EMPD
MMS, full thickness skin graft
Pelvic MRI w/ contrast, evaluated for sphincter and rectal involvement (-); colonoscopy showed hypertrophic anal condyloma; ref. for colposcopy
Imiquimod 5% 5x/ wk for 6 wks post-op;

SCC in situ

- Full genital exam revealed condyloma between vaginal introitus and anus
- Pelvic MRI w/ endocoil and contrast, evaluated for sphincter and rectal involvement (-)
- Colonoscopy showed hypertrophic anal condyloma; colposcopy wnl



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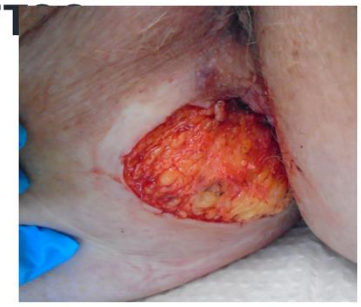
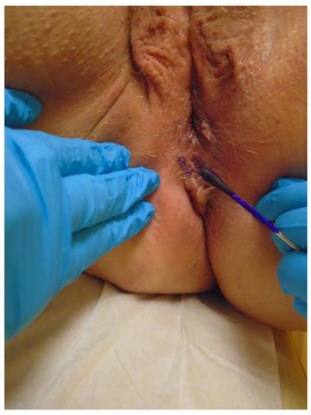
SCC in situ

- S/P MMS 2 stages, FT
- Post-op Imiquimod 5%, 5x/wk 6 wks
- Recommend colonoscopy 3 yrs
- Annual colposcopy



S/p MMS defect



S/p FTSG (9mo)

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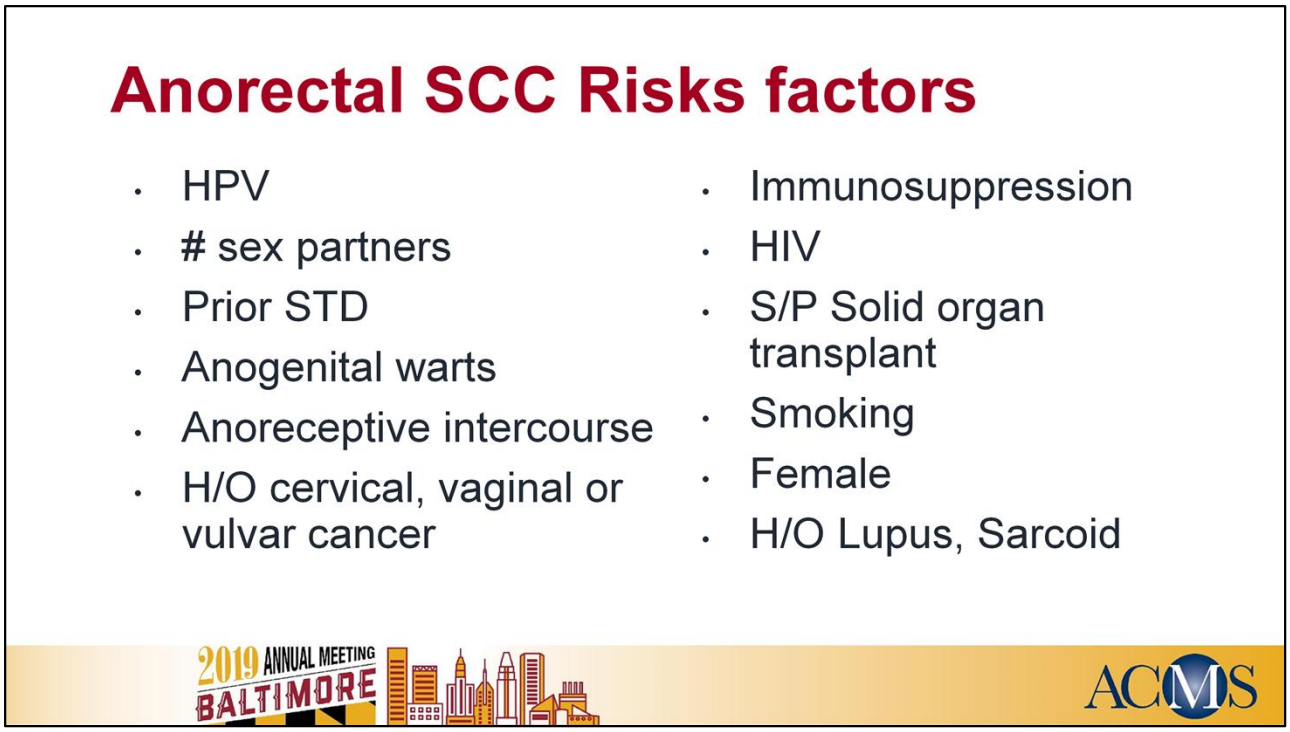
Imiquimod 5% 5x/ wk for 6 wks post-op;

Anorectal Squamous Cell Carcinoma

Actuarial survival rate:

- 5-yr survival rate: <50 y/o (87%), >50 y/o (53%)
  - Stage I (76%)
  - Stage II (37%)
  - Stage III (17%)
  - Stave IV (0%)*
  - * Patients w/ Stage IV did not survive +3 years.
- Patients >50 y/o more likely to have regional disease or metastasis
- Perineural invasion affects survival, not margin distance
- Tumor size prognostic indicator - even with negative lymph nodes



≈50% of patients with anal cancer present with localized, node-negative disease, which is associated with high cure rates; one third of patients will present with node-positive disease, whereas only 10% to 15% will present with distant metastases.8 Thus, even without effective preventative measures, the majority of patients with anal cancer are potentially curable at the time of diagnosis and treatment.

The multiple risk factors associated with developing squamous cancers of the anus are well documented and can be grouped into the 2 broad categories of HPV and immunosuppression, although there is also an association between these categories as well. Among the HPV-related risk factors include lifetime number of sexual partners,9 a history of previous sexually transmitted diseases of any kind,10 a history of anogenital warts,11 anoreceptive intercourse,12 and a history of cervical, vaginal, or vulvar cancer.13 Risk factors related to immunity include a HIV,14 autoimmune disorders such as lupus and sarcoidosis,15 and being the recipient of a solid organ transplant.16 Female sex3 and cigarette smoking17 are also associated with developing anal malignancies diagnosis of HIV,14 autoimmune disorders such as lupus and sarcoidosis,15 and being the recipient of a solid organ

transplant.16 Female sex3 and cigarette smoking17 are also associated with developing anal malignancies.

ANATOMIC CONSIDERATIONS AND TERMINOLOGY

The management of anal cancers requires a multidisciplinary approach, and the unfamiliarity of nonsurgical disciplines with anorectal anatomy can create ambiguity in describing the location and the clinical stage of anal cancers across disciplines. The anal canal, as viewed by

Anorectal SCC Work- up

- Women: Cervical PAP, colposcopy,
- Men: Penile exam
- Men & Women: High resolution Anoscopy
- No increased risk of Colon Ca but < 15% with colorectal neoplasms
- Colonoscopy to R/O synchronous colorectal neoplasm

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Although anal cancer is not a risk factor for the development of colon cancer, colorectal neoplasms have been demonstrated in15% of patients with anal cancer; therefore, colonoscopy should be performed to rule out synchronous colorectal neoplasms.88,89
Women should undergo a cervical Pap test, and men should undergo penile examination to exclude premalignant or malignant lesions. Although the immunohistochemical expression of p16 and Ki-67 has been shown to correlate with the degree of anal intraepithelial neoplasia,89 their role in the evaluation of anal SCC is still being defined.
Endoscopic and radiologic evaluation should be performed to help determine tumor extension and assess for metastatic disease. Grade of Recommendation: Strong recommendation based on low-quality evidence, 1C.
Biopsy should be performed under direct vision or with anoscopy. Although anal cancer is not a risk factor for the development of colon cancer, colorectal neoplasms have been demonstrated in <15% of patients with anal cancer; therefore, colonoscopy should be performed to rule out synchronous colorectal neoplasms.88,89 A CT of the chest, abdomen, and pelvis with intravenous contrast enhancement should be performed to evaluate for distant metastatic disease and

lymphadenopathy, including e

Anorectal Carcinoma Surveillance

- Digital rectal exam, high- resolution anoscopy, imaging depending on stage
- Visual and palpation exams Q3-6 months 1st yr, then anually

- CT of the chest, abdomen, and pelvis annually x3yrs if T3-T4 or inguinal node (+)
- Imaging begins 3 mo. post-CRT after fibrosis distinguishable from residual tumor
- Continue 5yrs post tx

CT
of the chest, abdomen, and pelvis annually for 3 years (if T3–T4 or inguinal node positive).
Surveillance involving digital rectal examination, anoscopy, and imaging should be continued for 5 years after completion of CRT. Grade of Recommendation: Strong recommendation based on moderate-quality evidence, 1B.
After the first evaluation post-CRT, additional surveillance including digital anorectal examination, anoscopy, and palpation of inguinal lymph nodes every 3 to 6 months for those in complete remission or every 4 weeks until remission <6 months is recommended in patients with evidence of persistent disease.134 Patients with residual changes require close follow-up and documentation. Surveillance involving digital rectal examination, anoscopy, and imaging should be continued for 5 years after completion of CRT. Grade of Recommendation: Strong recommendation based on moderate-quality evidence, 1B.

Extramammary Paget's Disease

Peak age 50-80

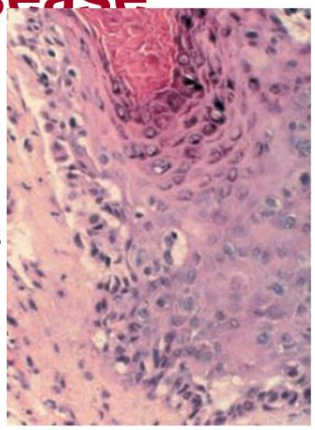
Women > Men

Erythematous, hyperkeratotic, pruritic plaques
Median size 6.5 cm

Histology similar to mammary Paget's disease

25% underlying cancer

Vulvar lesions: 60% Labia



EMPD of the left groin

(Leelavathi 2016)(Shieh 2002)(Damavandy 2017)(Chan 2012)(Zampogna 2002)(Machida 2015)(Takamichi 2015)

Postmenopausal women & men >50y/o; (Leelavathi)
Histologically similar to mammary Paget's disease
Anogenital presentation; apocrine gland-bearing skin
42% of EMPD Pts have non-cutaneous malignancy

Extramammary Paget's Disease

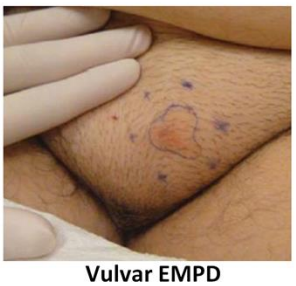
Prognosis related to tumor thickness

(>3mm) 5-year survival rate	57%
(1-3mm)	90%
(<1mm) and intermediate	99%

30-60% recurrence rate for EMPD treated with surgery.

MMS	(12%) 5-yr recurrence
WLE	(50%) 5-yr recurrence
WLE	2x higher recurrence rate vs MMS

Penile EMPD



Vulvar EMPD

Dose dependant response to imiquimod 5%
Complete response (CR) rate of 9.8% (2 months), 31.1% (4 mo.), and 71.6% (6mo.)

Increased treatment frequency improved CR:
5-7 treatments/ week (90.9%)

(Leelavathi 2016)(Shieh 2002)(Damavandy 2017)
(Chan 2012)(Zampogna 2002)(Machida 2015)(Takamichi 2015)

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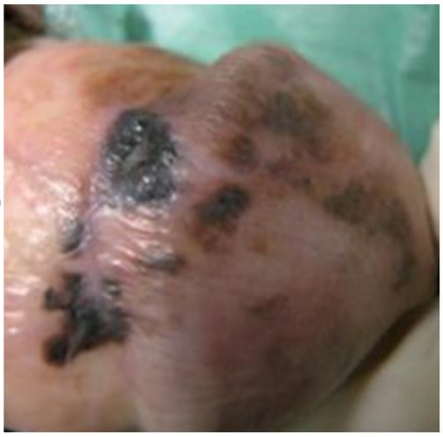
Postmenopausal women & men >50y/o; (Leelavathi)
Histologically similar to mammary Paget's disease
Anogenital presentation; apocrine gland-bearing skin
42% of EMPD Pts have non-cutaneous malignancy

Malignant Melanoma

Mucosal melanoma 0.03% cancer diagnoses

- **More frequent in women (65%)**
- **Genital tract (18%), anal/rectal (24%), urinary tract (3%)**
- **Peak age 70-79 (vs 50-69 in cutaneous MM)**
- **Often lack of melanin pigmentation**
- **Typically presents on glans (55%), prepuce (28%), penile shaft (9%), urethral meatus (8%)**
- **Survival rate 2-yr (63%) vs 5-yr (31%)**
- **~50% of cases thicker than 4mm**



MM of the penis

96,480 people/ yr diagnosed with MM (7.5% mortality)

Vulvar BCC <1% of BCCs; <5% of vulvar cancers (Fleury + De Giorgi)
Penile BCC 0.03% of BCCs in men (Roewe)
Perianal BCC 1% of BCCs; 0.2% of anorectal cancer (Bulur)
Vulvar SCC 4% of female genital malignancy (Herr)
Precancerous lesion may become SCC (Khieu)
Anogenital presentation;
Type 16 + 18 (+ 31, 33, 35, 39, 45, 51, 52, 54, 56, 58, 59, 66, 68, 69) HPV associated with oncogenesis
Cause of 45% of penile carcinoma (Greenberg)
HPV DNA found in 50% of vulvar carcinoma
Penile SCC <1% of NMSC (Greenberg)
Perianal SCC 1.5% of GI cancer (Uronis)
Postmenopausal women & men >50y/o; (Leelavathi)
Histologically similar to mammary Paget's disease
Anogenital presentation; apocrine gland-bearing skin
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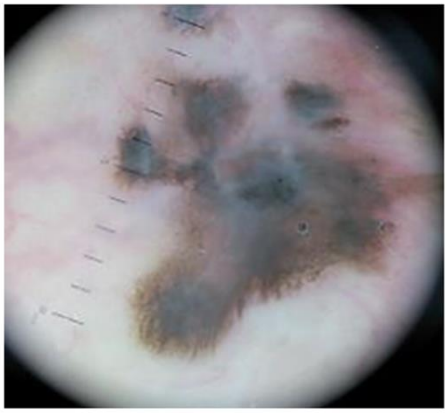
Malignant Melanoma - women

- **5-yr survival,10-47% for female genital MM because of depth and dx**
- **Higher proportion (85%) are invasive (median thickness 8.6mm)**
- **30% rate of oncogenic mutation (BRAF, NRAS, & KIT)**
- **Increased risk recur. + lymph node mets**



MM under dermoscopy

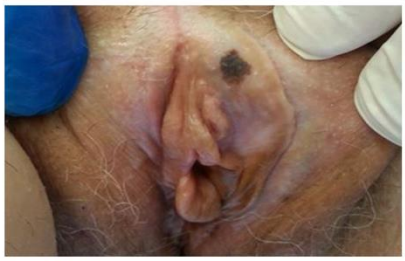
(De Giorgi)(Demitsu 2000)(De Giorgi 2010)(Patrick 2007)(Udager 2017)(Kostaki 2018)

96,480 people/ yr diagnosed with MM (7.5% mortality)

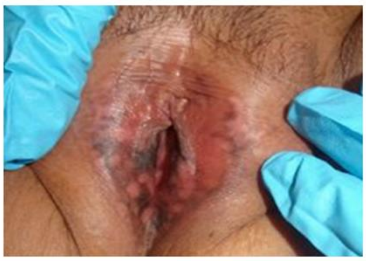
Vulvar BCC <1% of BCCs; <5% of vulvar cancers (Fleury + De Giorgi)
Penile BCC 0.03% of BCCs in men (Roewe)
Perianal BCC 1% of BCCs; 0.2% of anorectal cancer (Bulur)
Vulvar SCC 4% of female genital malignancy (Herr)
Precancerous lesion may become SCC (Khieu)
Anogenital presentation;
Type 16 + 18 (+ 31, 33, 35, 39, 45, 51, 52, 54, 56, 58, 59, 66, 68, 69) HPV associated with oncogenesis
Cause of 45% of penile carcinoma (Greenberg)
HPV DNA found in 50% of vulvar carcinoma
Penile SCC <1% of NMSC (Greenberg)
Perianal SCC 1.5% of GI cancer (Uronis)
Postmenopausal women & men >50y/o; (Leelavathi)
Histologically similar to mammary Paget's disease
Anogenital presentation; apocrine gland-bearing skin
42% of EMPD Pts have non-cutaneous malignancy

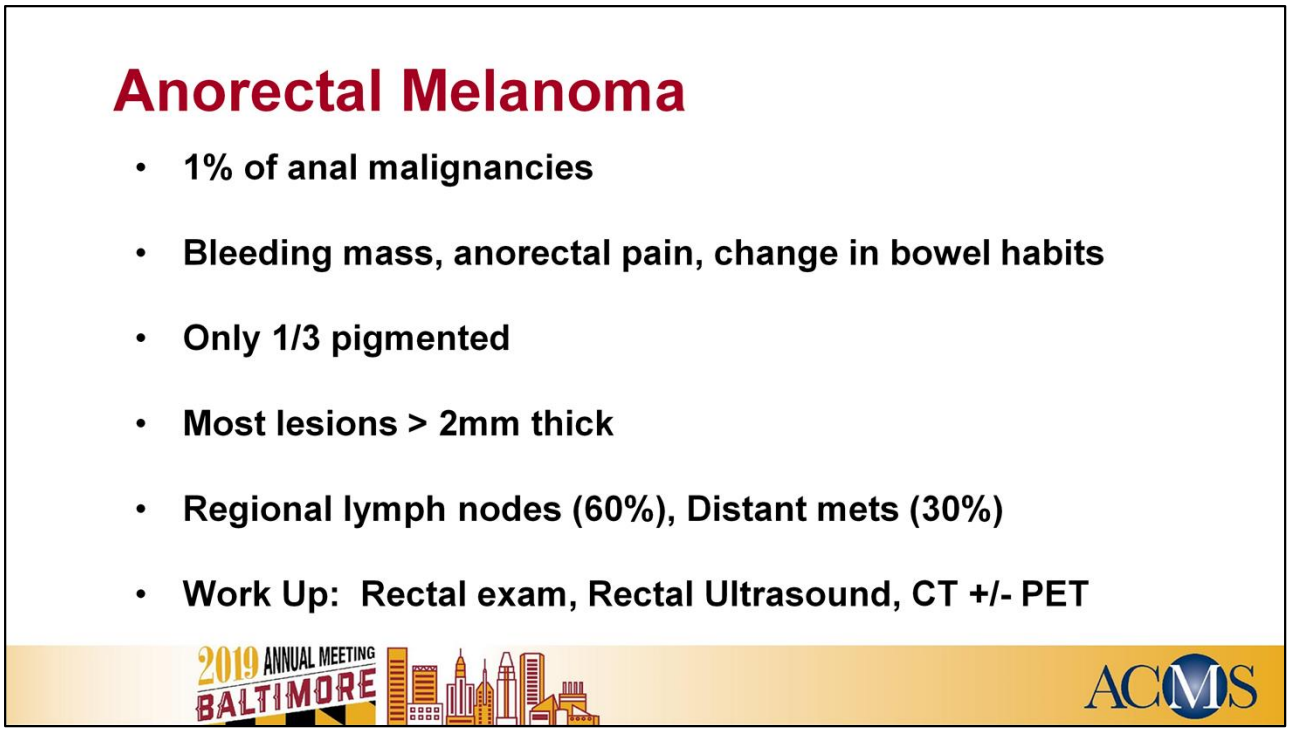
Vulvar Melanoma vs. Melanosis

- Average age 60-70
- 2-10% of all vulvar neoplasms (2nd most comm)
- Acral lentiginous, then nodular most common
- Labia minora, clitoris most common; may be multifocal
- 5 yr survival less than 50%
- 25% amelanotic; 6% pre-existing nevi



- Women in 40's
- Lichen sclerosis may predispose
- Mucous membranes rather than keratinized skin
- Labia Minora



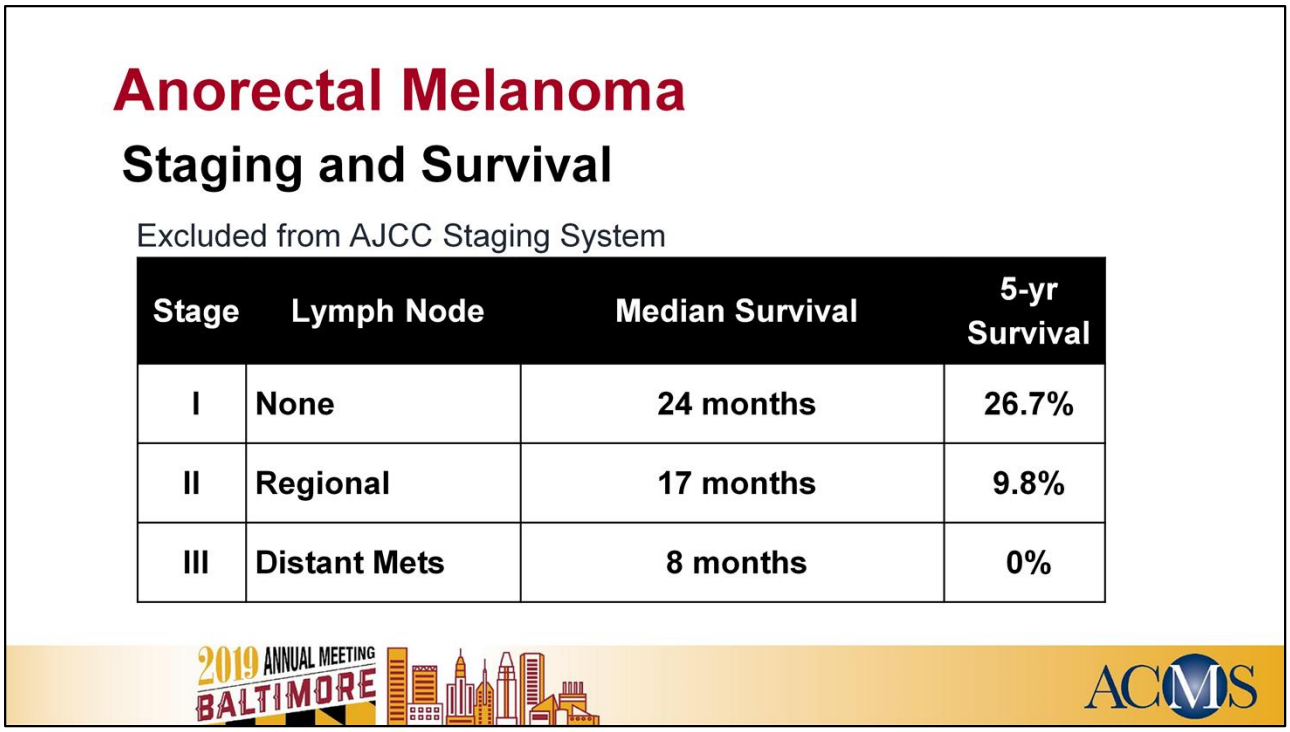


Patients typically present with bleeding, a mass, anorectal pain, or a change in bowel habits. Occasionally, melanoma is an incidental finding on pathologic evaluation of a hemorrhoidectomy or anal polyp specimen. Anorectal melanoma is pigmented in only one-third of cases. Most patients present with lesions that are >2 mm thick. Regional lymph node involvement is found in approximately 60 percent of patients at presentation [1], and distant metastases are present at diagnosis in approximately 30 percent of cases [95-100].

The initial evaluation of patients with anorectal melanoma should include a rectal examination, rectal ultrasound, and CT and/or PET imaging to assess for distant metastases.

Anorectal melanoma is excluded from the American Joint Committee on Cancer (AJCC) staging system for anal cancers. Retrospective series have used a simple system in which localized disease only, regional lymph node involvement, and distant metastases are classified as stages I, II, and III, respectively [101].

Patients with lymph node metastases or distant metastases at presentation have an especially poor prognosis. A review of 183 patients with anorectal mucosal melanoma identified in the Surveillance, Epidemiology, and End



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- Stage I – median survival, 24 months; 5-year survival, 26.7 percent
- Stage II – median survival, 17 months; 5-year survival, 9.8 percent

- Stage III – median survival, 8 months; 5-year survival, 0 percent

Factors that may adversely affect prognosis in patients with localized disease include the presence of perineural invasion, tumor size and thickness, and the presence of amelanotic melanoma [96,97,102-104].

Pearls

Biopsy new or unresolving genital plaque

- **25% of genital melanoma are unpigmented**
- **Multifocal sampling of large lesions**

Perform complete genital exam with newly diagnosed genital cancer

Genital SCC: Request HPV(+/-) on pathology

- **Refer for Colposcopy and Cystoscopy, Colonoscopy**

Vaginal Melanoma: Follow with colposcopy

Work with urology, gynecology, colo-rectal for follow-up. These patients need long-term surveillance!

ACMS

Stigma, Detection Delay, Patient Education, Clinician Resources, Specialist Referral, Uncommon Diagnoses, (Misconceptions + Misdiagnosis)

Thank you

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