外阴癌的流行病学、诊断、组织病理学及治疗

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文献评审有效期至： 2024-11.
专题最后更新日期： 2024-08-28.

There is a newer version of this topic available in English. 该专题有一个更新版本英文版本。

引言

外阴癌比其他妇科恶性肿瘤少见，包括宫体癌、卵巢癌和宫颈癌；在美国，外阴癌也比阴道癌少见[1]。最常见的外阴癌组织学类型是鳞状细胞癌，占比不低于75%[2,3]。其他组织学类型包括黑素瘤、基底细胞癌、前庭大腺腺癌、肉瘤和Paget病 (表 1)。

HPV感染与大部分外阴鳞状细胞癌有关。外阴硬化性苔藓也与外阴癌风险增加有关。

本文将总结外阴癌的流行病学、临床表现、诊断及组织学。本专题将介绍外阴癌的一般治疗推荐，详见其他专题。外阴鳞状细胞癌的分期、治疗及预后也见其他专题。(参见 “外阴鳞状细胞癌的分期和手术治疗” 和 “外阴鳞状细胞癌的内科治疗与预后”)

流行病学

在美国，每年约新增6900例外阴癌病例，每年约有1630人死于外阴癌[1]。

2010-2014年美国各种族或族群的外阴癌发病率如下：非西班牙语裔白人(2.7/100,000)、非西班牙语裔黑人(1.8/100,000)、美国亚裔/太平洋岛裔(0.9/100,000)、西班牙语裔美国人(1.8/100,000)、非西班牙语裔美国人(2.6/100,000)[4]。在美国，一些数据表明黑人患者出现外阴癌时的年龄较小，出现远处播散的概率较大，在不同肿瘤模型中均存在该情况[5,6]。

美国女性确诊外阴癌的终生风险为0.3%[4]。美国外阴癌的平均确诊年龄为68岁。2010-2014年外阴癌病例的年龄分布如下：

- <20岁 – 0.1%
- 20-34岁 – 1.8%
- 35-44岁 – 5.5%
- 45-54岁 – 14.6%
- 55-64岁 – 20.4%
- 65-74岁 – 21.3%
- 75-84岁 – 21.4%
- ⩾85岁 – 15%

多数外阴癌患者确诊时处于早期阶段，确诊时病情阶段分布如下：局限于原发部位(59%)、播散至局部器官和淋巴结(30%)、远处转移(6%)[4]。在美国，确诊外阴癌后5年生存率为72.1%，死亡年龄的中位数为78岁。

外阴癌最常见的组织学类型是鳞状细胞癌。多数有关发病率和患病率的数据都是针对外阴癌整体，而不仅仅是鳞状细胞癌。(参见下文‘组织学类型’)

危险因素和病因

外阴癌的危险因素包括外阴或宫颈上皮内瘤变、宫颈癌既往史、吸烟、外阴硬化性苔藓、免疫缺陷综合征和北欧血统[7,8]。

目前提出了两种独立的外阴鳞状细胞癌发病途径[9]：

- **与HPV相关** – HPV感染常与外阴癌有关。 一篇meta分析通过92项研究发现，外阴癌患者的HPV感染率为39%，以HPV16型感染最常见(78%)，其次是HPV33型(7.5%)[10]。$p16^{INK4a}$是HPV阳性的替代指标，大多数HPV阳性外阴癌患者的该指标也是阳性(73%)。

- **与HPV无关** – 这类外阴癌与慢性炎症(外阴营养不良)或自身免疫性问题有关[11-14]。 对于硬化性苔藓患者，有人提出分化型外阴上皮内瘤变(vulvar intraepithelial neoplasia, VIN)是外阴癌的前期病变[15,16]。 与HPV无关的外阴癌患者常有p53表达[9]。(参见 “外阴鳞状上皮内病变(外阴上皮内瘤变)”，关于‘危险因素和预防’一节)

HPV相关外阴癌的结局优于与HPV无关的外阴癌， 详见其他专题。(参见 “外阴鳞状细胞癌的内科治疗与预后”，关于‘预后’一节)

临床表现

外阴癌患者常有外阴病变，可由其本人或医生发现。外阴恶性肿瘤所有组织学类型的症状和体征都相似。很多患者确诊时没有症状，但部分患者会出现外阴瘙痒或出血。

外阴病变 — 多数患者表现为大阴唇单病灶外阴斑块、溃疡或肿块(肉样、结节状或疣状)；小阴唇、会阴、阴蒂和阴阜较少受累 (图片 1A 和 图片 1B 和 图片 1C)。10%的病例存在广泛病变，无法确定真正的原发灶 (图片 1D 和 图片 2)[17]。

5%的病例存在多灶性病变，因此应评估外阴和肛周的全部皮肤表面以及宫颈和阴道。多达22%的外阴恶性肿瘤患者同时存在第二恶性肿瘤，最常为宫颈瘤[18]。

外阴瘙痒 — 瘙痒是很多外阴病变的常见主诉，存在基础外阴皮肤病(如，硬化性苔藓或扁平苔藓)时尤其常见 (表 2)。(参见 “外阴硬化性苔藓的临床表现和诊断”)

其他表现 — 一些患者可出现外阴出血或疼痛。不太常见的症状包括二便困难、直肠出血、腹股沟淋巴结肿大或下肢水肿，此类症状提示晚期疾病。

诊断性评估

诊断性评估旨在检出外阴病变，并确定是否需行活检。外阴癌的诊断性评估包括：

- 外阴癌的危险因素史或症状史，以及可影响治疗的因素史。
- 完整的妇科检查，需注意视诊并触诊外阴及腹股沟，以确定有无病变、颜色改变、肿块或溃疡。
- 对肉眼可见且疑似外阴癌的病变进行活检 (图片 1A-D 和 图片 3)。病变外观各异，可能为单发或多发。鳞状细胞癌病变通常呈坚硬、白色、红色或肤色的丘疹、结节或斑块。可见不同程度的糜烂或溃疡形成，其表面容易破溃。(参见 “外阴病变：水疱、大疱、糜烂和溃疡的鉴别诊断” 和 “外阴病变的诊断性评估”，关于‘操作步骤’一节)
- 必要时使用阴道镜检查外阴，以发现肉眼检查未识别的亚临床病变。(参见 “阴道镜概述”，关于‘阴道镜检查外阴’一节)

总体上，该诊断性评估与疑似VIN患者的诊断性评估类似。VIN的诊断性评估详见其他专题。(参见 “外阴鳞状上皮内病变(外阴上皮内瘤变)”，关于‘诊断性评估’一节)

诊断

外阴癌是根据外阴活检做出的组织学诊断。不应仅根据肉眼可见的表现或阴道镜表现做出诊断。

鉴别诊断

外阴癌的鉴别诊断包括其他外阴病变。

必须区分外阴癌与VIN，后者与外阴鳞状细胞癌的表现可能类似或相同，只能根据活检来鉴别。

外阴黑素瘤罕见，但却是更常见的外阴癌非鳞状组织学类型。外阴色素性病变有多种病因，常见病因包括黑素细胞痣或血管角皮瘤 (表 3)。应检查并评估外阴色素性病变，以确定是否需行活检。外阴黑素瘤的形态详见其他专题。(参见 “外阴色素沉着性(黑色、棕色、蓝色)病变的鉴别诊断”)

表现为白色斑片或斑块的外阴皮肤病也可能与外阴癌表现类似，包括硬化性苔藓或扁平苔藓。(参见 “外阴硬化性苔藓的临床表现和诊断”和 “外阴扁平苔藓”)

与外阴癌表现类似的其他病变包括：表皮包涵囊肿、尖锐湿疣(生殖器疣)、前庭大腺疾病、软垂疣、脂溢性角化病、汗腺瘤。如果最初怀疑为其中一种疾病，但相应治疗无效，则应进行活检。

外阴病变的鉴别诊断详见其他专题。(参见 “外阴病变：水疱、大疱、糜烂和溃疡的鉴别诊断”)

组织学类型

鳞状细胞癌是外阴癌最常见的组织学类型，占比不低于75%[2,3]。其他组织学类型包括黑素瘤、基底细胞癌、前庭大腺腺癌、肉瘤和Paget病 (表 1)。一项荷兰癌症注册研究阐明了组织学类型的典型分布，研究时期为1989-2010年，纳入了5680例外阴癌患者：鳞状细胞癌(81%)、基底细胞癌(8%)、黑素瘤(6%)、其他组织学亚型(5%)[2]。

鳞状细胞癌 — 至少75%的外阴恶性肿瘤为鳞状细胞癌[2,3]，有两种亚型，通常均发生于阴唇或前庭：

- 角化型、分化型或单纯型较常见，发生于年龄较大患者，与HPV感染无关，但与外阴营养不良(如硬化性苔藓)有关，在资源有限的国家还与慢性性病肉芽肿病变有关 (图片 4)。
- 经典型、疣型或Bowenoid型主要与HPV 16、HPV 18和HPV 33感染有关，见于较年轻患者[19,20]。HPV感染相关的危险因素包括初次性行为时年龄较小、多个性伴侣、HIV感染和吸烟。这些患者往往在疾病早期就诊[21]，但已报道过数例发生Ⅲ/Ⅳ期外阴癌的HIV感染者[22]。

  宫颈癌也与持续存在HPV感染密切相关[23]。此外还有证据表明，一些高分级的VIN和阴道上皮内瘤变是来源于高分级或恶性宫颈疾病的单克隆病变[24]。存在宫颈可能不是致瘤性HPV感染生殖道的必要条件。无论患者是否接受过子宫切除术，阴道中致瘤性HPV亚型的检出率都相近[25]。(参见 “人乳头瘤病毒感染的病毒学及与癌症的关系”)

疣状癌 — 外阴疣状癌是一种具有独特特征的鳞状细胞癌变异型。虽然癌灶外观呈菜花样，但其是由病变基底部活检显示的疣状结构鳞状细胞癌分化而来，活检表现为叶状乳头样结构，无尖锐湿疣典型的中央型结缔组织核成分。病变生长缓慢，很少转移至淋巴结，但可能引起局部破坏。

基底细胞癌 — 这是鳞状组织学类型，但与外阴鳞状细胞癌不同 (表 1)。2%-8%的外阴癌是基底细胞癌，而2%的基底细胞癌发生于外阴[2,26]。

外阴基底细胞癌通常累及绝经后的白人患者，病变可能呈局部浸润，但通常不转移[27,28]。典型外观为“蚕蚀性溃疡”，其边缘呈围堤状隆起，中央有溃疡形成；病变可能有色素沉着，或呈白珍珠色和灰色。患者常无症状，但可能出现瘙痒、出血或疼痛。

基底细胞癌患者身体其他部位出现前驱性或并发性恶性肿瘤的风险较高[28]。因此，应进行针对其他原发性恶性肿瘤的全面检查。(参见 “基底细胞癌的流行病学、发病机制、临床特征和诊断”)

黑素瘤 — 这是第二常见的外阴癌组织学类型，在原发性外阴肿瘤中占2%-10%[27,29-31]。

外阴黑素瘤主要见于绝经后的非西班牙语裔白人患者，中位年龄为68岁(范围为10-99岁)[30]。相比之下，其他部位的皮肤黑素瘤常发生于45岁前。(参见 “黑素瘤的流行病学和危险因素”，关于‘流行病学’一节)

根据1985-1994年美国国家癌症数据库统计，女性生殖道黑素瘤占所有黑素瘤的0.02%，占黏膜黑素瘤的18%[32]。

外阴黑素瘤通常呈色素性病变，但也可发生无色素性病变。多数病变新发于阴蒂或小阴唇，但也可见于既已存在的交界痣或复合痣内[33]。(参见 “外阴色素沉着性(黑色、棕色、蓝色)病变的鉴别诊断”，关于‘黑素瘤’一节)

外阴黑素瘤的诊断与治疗详见其他专题。(参见 “原发性皮肤黑素瘤或其他少见部位黑素瘤的手术治疗”)

肉瘤 — 1%-2%的外阴恶性肿瘤为软组织肉瘤，包括平滑肌肉瘤、横纹肌肉瘤、脂肪肉瘤、血管肉瘤、神经纤维肉瘤、上皮样肉瘤和未分化/未分类的软组织肉瘤[34]。患者的预后通常较差[35,36]。

与位于四肢和躯干的软组织肉瘤一样，在外阴软组织肉瘤中，存在浸润性边缘、有丝分裂速度较快且直径＞5cm的高分级病变最有可能复发。(参见 “软组织肉瘤的临床表现、组织病理学、诊断性评估及分期”，关于‘预后因素’一节)

外阴Paget病 — 乳房外Paget病是一种上皮内腺癌，在所有外阴恶性肿瘤中的占比<1%[37]。多数患者为60-79岁的白人。

瘙痒是最常见的症状，见于70%的患者，但也有患者无症状[38]。 检查显示，外阴Paget病的外观与乳房Paget病相似(参见 “乳房Paget病”)。病变呈红色湿疹样，边界清楚，边缘轻微隆起，红色背景中常分布有苍白的小岛样结构 (图片 5)。外阴Paget病通常呈多灶性，可见于外阴、阴阜、会阴/肛周区或大腿内侧的任意部位。也有病变侵及阴道的报道[39]。

诊断依据是特征性组织病理学表现 (图片 6A-B)。存在疑似病变的患者应接受外阴活检，包括在接受恰当抗湿疹治疗6周内未缓解的持续性瘙痒性湿疹病变患者。

小型研究显示，多达25%的患者在表面病变之内或之下可能存在浸润性腺癌 (图片 7A-B)[37,40-43]。由于20%-30%的外阴Paget病患者存在非邻接癌，例如乳腺、直肠、膀胱、尿道、宫颈或卵巢

癌，故应评估其他部位可能同时存在的肿瘤[44]。可完善乳腺X线钼靶摄影、结肠镜、尿细胞学和/或经阴道超声等检查[45]。

前庭大腺癌 — 占所有外阴癌的0.1%-5%，占所有女性恶性肿瘤的0.001%[46]。一项研究显示，绝经前人群前庭大腺癌的发病率为0.023/100,000人年，绝经后人群前庭大腺癌的发病率为0.114/100,000人年[47]。60-69岁人群的前庭大腺癌发病率最高。多数患者没有良性前庭大腺疾病的既往史。

前庭大腺起源的癌症最常为腺癌或鳞状细胞癌，但也可能发生移行细胞癌、腺鳞癌和腺样囊性癌[48,49]。多数原发性外阴腺癌发生于前庭大腺。只有前庭大腺鳞状细胞癌与HPV感染有关[48]。

前庭大腺癌常发生转移，因为该区域富含血管和淋巴网。一项纳入11例前庭大腺癌患者的研究显示，55%的患者疾病复发，5年生存率为67%[50]。仅有的2例单纯外阴复发患者的无瘤生存时间分别为8个月和180个月。

前庭大腺癌与良性前庭大腺肿块的鉴别详见其他专题。

治疗

鳞状细胞癌 — 治疗取决于外阴病变范围和淋巴结评估结果，详见其他专题。(参见 “外阴鳞状细胞癌的分期和手术治疗”和 “外阴鳞状细胞癌的内科治疗与预后”)

疣状癌 — 根治性局部切除治疗通常足够，因为疣状癌为局部浸润病变，但偶尔会转移。应对可疑淋巴结进行活检，若结果为阳性，则需行腹股沟淋巴结切除清扫。禁用放射治疗(radiation therapy, RT)，因为放疗可诱发间变性转化，增加病灶转移的可能性，但目前鲜有证据支持该观点。复发的疣状癌通常经手术治疗。

基底细胞癌 — 局部侵袭性病变，偶尔会转移。因此，不行淋巴结切除清扫的根治性局部切除即可充分治疗。(参见 “低复发风险基底细胞癌的治疗和预后”)

黑素瘤 — 治疗详见其他专题。(参见 “局部区域黏膜黑素瘤的流行病学、临床诊断和治疗”，关于‘外阴阴道黑素瘤’一节)

肉瘤 — 较常见的组织学类型包括血管黏液瘤[51]和横纹肌肉瘤，后者通常在儿童中确诊[52]。(参见 “儿童、青少年及成人横纹肌肉瘤的治疗”，关于‘手术的作用’一节)

局部扩大切除术是治疗多数外阴肉瘤的标准方法。淋巴转移不常见[51,53](参见 “儿童、青少年及成人横纹肌肉瘤的治疗”，关于‘手术的作用’一节)。手术治疗常与术前或术后放疗相配合，这与解剖部位无法实现较宽手术切缘(在不发生截肢等重大致残性后果的情况下)的四肢和躯干软组织肉瘤的治疗类似。

外阴Paget病 — 外阴是乳房外Paget病最常见的部位之一。治疗一般包含局部扩大切除术或外阴切除术，具体视病变范围而定，但已报道特定患者(如老年、体能状态差)接受更保守的手术治疗[54]。

无需进行根治性切除，但切缘最好为2cm。浸润较深和淋巴血管受累提示预后较差[53]。有人建议对存在浸润性病变或基础腺癌的患者进行腹股沟淋巴结切除清扫[55]。

12%-58%的患者会出现局部复发，即使手术切缘阴性也可能复发，据推测这是由于病灶呈多中心性，以及显微镜下浸润超过临床上可见的边缘[38,40,41,56]。为实现显微镜下切缘干净，可能需切除距可见肿瘤边缘5cm内外观正常的皮肤[57]。荧光素定位[58]或Mohs显微外科手术治疗(即，显微镜控制下系统性切除癌组织)或可降低复发率，尤其是复发性肿瘤[53,57,59-61]。Mohs显微外科手术技术的完整描述详见其他专题。(参见 “Mohs手术”)

目前没有数据表明辅助放疗对外阴Paget病的益处。根治性放疗、细胞毒化疗和局部用咪喹莫特治疗外阴Paget病的作用也不明确，但某些患者可以尝试[53,62-69]。目前已报道过人类表皮生长因子受体2(human epidermal growth factor receptor 2, HER2)过表达[70,71]。

由于复发风险较高及非邻接癌风险增加，需进行长期随访。在多达25%的患者中，Paget病与基础浸润性腺癌有关[37,40-43]，另有20%-30%的患者将发现或出现其他非外阴腺癌[37,40]。一项研究显示，8%的非浸润性外阴Paget病患者在中位5年后进展为浸润性外阴病变，但至少有部分、甚至全部病例均可能是新发浸润性病变，而不是非浸润性病变进展所致[41]。每年都应进行外阴视诊，并放宽进行活检的条件。应考虑筛查和监测其他部位的肿瘤，例如乳腺、肺、结直肠、胃、胰腺和卵巢的肿瘤。(参见 “乳腺癌筛查的策略和推荐”和 “结直肠癌筛查：一般风险人群的筛查策略”)

前庭大腺癌 — 原发性前庭大腺癌罕见，占所有外阴癌的0.1%-5%，占所有女性恶性肿瘤的0.001%[46]。一项研究显示，绝经前人群前庭大腺癌的发病率为0.023/100,000人年，绝经后人群前庭大腺癌的发病率为0.114/100,000人年[47]。60-69岁人群的前庭大腺癌发病率最高。多数患者没有良性前庭大腺疾病的既往史。

约50%的前庭大腺癌为鳞状组织学类型，起源于前庭大腺腺管，而不是前庭大腺。其余前庭大腺癌涉及多种罕见腺癌，包括腺样/囊性癌，其惰性自然病程、神经周浸润倾向及不常播散至淋巴结等行为与唾液腺腺样/囊性癌的行为相似[72,73]。

前庭大腺癌通常位于外阴深部 (图 1)，并且由于肉眼检查可发现该病变时已处于病程晚期，故常常延误诊断。其最常见的表现为无痛性外阴肿块，而前庭大腺复合体肿块常被误诊为脓肿或囊肿。肿块可能为实性、囊性或脓性，或为可在前庭大腺囊肿内触及的实性包块。前庭大腺肿块固定于包块下方的组织时，应考虑为恶性肿瘤。蔓延至上覆皮肤是一种晚期表现，通过前庭大腺腺管蔓延至阴道继而出血通常仅见于巨块病变。

完整切除病灶常需广泛深入清除。传统疗法为根治性外阴切除术，并进行双侧腹股沟和盆腔淋巴结切除清扫。范围较小的根治性切除术可能也有效，例如根治性局部切除术或部分外阴切除术联合同侧腹股沟淋巴结切除清扫[49,74]。由于原发灶接近肛门直肠和耻骨弓，手术切缘通常镜检阳性，需行术后放疗以降低局部复发率[49]。

对于前庭大腺原发癌患者，初始放化疗或近距离治疗也许能保留直肠功能或完全避免手术需求[75-78]。放化疗对鳞状组织学类型的前庭大腺癌特别有效。如果同侧腹股沟淋巴结受累，进行盆腔和双

侧腹股沟放疗可降低区域复发率。一些单独的病例报告称，聚乙二醇化多柔比星脂质体[64]和紫杉醇[79]对晚期疾病有效。

由于外阴富含血管和淋巴网，前庭大腺癌常发生转移。但一项总结了30年临床经验并纳入了36例前庭大腺癌患者的研究报道，5年生存率为85%[49]。

学会指南链接

部分国家及地区的学会指南和政府指南的链接参见其他专题。(参见 “Society guideline links: Vulvar cancer and vaginal cancer”)

总结与推荐

- **流行病学** – 外阴癌是美国第四常见的妇科恶性肿瘤，排在子宫癌、卵巢癌及宫颈癌之后。美国每年约新增6900例外阴癌病例，每年约有1630人死于外阴癌。(参见上文‘流行病学’)

  美国女性确诊外阴癌的终生风险为0.3%。美国外阴癌平均确诊年龄为68岁。多数外阴癌患者确诊时处于早期阶段，约60%的病变局限于原发部位。确诊后5年生存率为72.1%，死亡年龄的中位数为78岁。(参见上文‘流行病学’)

- **组织学类型** – 鳞状细胞癌是外阴癌最常见的组织学类型，占比不低于75%[2,3]。其他组织学类型包括黑素瘤、基底细胞癌、前庭大腺腺癌、肉瘤和Paget病 (表 1)。(参见上文‘流行病学’和‘组织学类型’)

- **危险因素** – 包括外阴或宫颈上皮内瘤变、宫颈癌既往史、吸烟、外阴硬化性苔藓以及免疫缺陷综合征。目前已提出的外阴鳞状细胞癌致病途径有2种：HPV感染、慢性炎症或自身免疫过程。(参见上文‘危险因素和病因’)

- **临床表现** – 外阴癌患者常表现为外阴病变，可由患者或医生发现。很多患者确诊时没有症状，但部分患者会出现外阴瘙痒或出血。如果患者主诉腹股沟肿块或泌尿道/下消化道症状，提示病情处于晚期。(参见上文‘临床表现’)

- **诊断** – 外阴癌是基于外阴病变活检的组织学诊断。诊断性评估旨在检出外阴病变，并确定是否需行活检。评估包括寻找外阴癌症状史及危险因素，进行妇科检查并仔细识别病变和描述其特点，可能需行阴道镜检查，以及进行活检。(参见上文‘诊断’和‘诊断性评估’)

- **鉴别诊断** – 包括外观类似的其他外阴病变。外阴癌的外观各异。鳞状细胞癌病变通常呈坚硬、白色、红色或肤色的丘疹、结节或斑块。可见不同程度的糜烂或溃疡形成，其表面容易破溃。黑素瘤是色素性病变。鉴别诊断包括外阴上皮内瘤变(VIN)、黑素细胞痣、血管角皮瘤、硬化性苔藓和尖锐湿疣(生殖器疣)。(参见上文‘鉴别诊断’)

- **治疗** – 本专题介绍外阴癌的一般治疗原则，详见其他专题。(参见上文‘治疗’)

致谢

UpToDate的编辑人员感谢John C Elkas, MD, JD对本专题早期版本做出的贡献。

参考文献

1. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. CA Cancer J Clin 2024; 74:12.
2. Schuurman MS, van den Einden LC, Massuger LF, et al. Trends in incidence and survival of Dutch women with vulvar squamous cell carcinoma. Eur J Cancer 2013; 49:3872.
3. Saraiya M, Watson M, Wu X, et al. Incidence of in situ and invasive vulvar cancer in the US, 1998-2003. Cancer 2008; 113:2865.
4. https://seer.cancer.gov/statfacts/html/vulva.html (Accessed on April 28, 2017).
5. Rauh-Hain JA, Clemmer JT, Bradford LS, et al. Racial disparities in cervical cancer survival over time. Cancer 2013; 119:3644.
6. Jagsi R, Abrahamse P, Hawley ST, et al. Underascertainment of radiotherapy receipt in Surveillance, Epidemiology, and End Results registry data. Cancer 2012; 118:333.
7. Madsen BS, Jensen HL, van den Brule AJ, et al. Risk factors for invasive squamous cell carcinoma of the vulva and vagina--population-based case-control study in Denmark. Int J Cancer 2008; 122:2827.
8. Brinton LA, Thistle JE, Liao LM, Trabert B. Epidemiology of vulvar neoplasia in the NIH-AARP Study. Gynecol Oncol 2017; 145:298.
9. Höhn AK, Brambs CE, Hiller GGR, et al. 2020 WHO Classification of Female Genital Tumors. Geburtshilfe Frauenheilkd 2021; 81:1145.
10. Li Z, Liu P, Wang Z, et al. Prevalence of human papillomavirus DNA and p16INK4a positivity in vulvar cancer and vulvar intraepithelial neoplasia: a systematic review and meta-analysis. Lancet Oncol 2023; 24:403.
11. de Koning MN, Quint WG, Pirog EC. Prevalence of mucosal and cutaneous human papillomaviruses in different histologic subtypes of vulvar carcinoma. Mod Pathol 2008; 21:334.
12. Halec G, Alemany L, Quiros B, et al. Biological relevance of human papillomaviruses in vulvar cancer. Mod Pathol 2017; 30:549.
13. Weberpals JI, Lo B, Duciaume MM, et al. Vulvar Squamous Cell Carcinoma (VSCC) as Two Diseases: HPV Status Identifies Distinct Mutational Profiles Including Oncogenic

Fibroblast Growth Factor Receptor 3. Clin Cancer Res 2017; 23:4501.

14. de Sanjosé S, Alemany L, Ordi J, et al. Worldwide human papillomavirus genotype attribution in over 2000 cases of intraepithelial and invasive lesions of the vulva. Eur J Cancer 2013; 49:3450.
15. van de Nieuwenhof HP, Bulten J, Hollema H, et al. Differentiated vulvar intraepithelial neoplasia is often found in lesions, previously diagnosed as lichen sclerosus, which have progressed to vulvar squamous cell carcinoma. Mod Pathol 2011; 24:297.
16. Bigby SM, Eva LJ, Fong KL, Jones RW. The Natural History of Vulvar Intraepithelial Neoplasia, Differentiated Type: Evidence for Progression and Diagnostic Challenges. Int J Gynecol Pathol 2016; 35:574.
17. Zacur H, Genadry R, Woodruff JD. The patient-at-risk for development of vulvar cancer. Gynecol Oncol 1980; 9:199.
18. Collins CG, Lee FY, Roman-Lopez JJ. Invasive carcinoma of the vulva with lymph node metastasis. Am J Obstet Gynecol 1971; 109:446.
19. Hildesheim A, Han CL, Brinton LA, et al. Human papillomavirus type 16 and risk of preinvasive and invasive vulvar cancer: results from a seroepidemiological case-control study. Obstet Gynecol 1997; 90:748.
20. Iwasawa A, Nieminen P, Lehtinen M, Paavonen J. Human papillomavirus in squamous cell carcinoma of the vulva by polymerase chain reaction. Obstet Gynecol 1997; 89:81.
21. Al-Ghamdi A, Freedman D, Miller D, et al. Vulvar squamous cell carcinoma in young women: a clinicopathologic study of 21 cases. Gynecol Oncol 2002; 84:94.
22. Elit L, Voruganti S, Simunovic M. Invasive vulvar cancer in a woman with human immunodeficiency virus: case report and review of the literature. Gynecol Oncol 2005; 98:151.
23. Bosch FX, Manos MM, Muñoz N, et al. Prevalence of human papillomavirus in cervical cancer: a worldwide perspective. International biological study on cervical cancer (IBSCC) Study Group. J Natl Cancer Inst 1995; 87:796.
24. Vinokurova S, Wentzensen N, Einenkel J, et al. Clonal history of papillomavirus-induced dysplasia in the female lower genital tract. J Natl Cancer Inst 2005; 97:1816.
25. Castle PE, Schiffman M, Bratti MC, et al. A population-based study of vaginal human papillomavirus infection in hysterectomized women. J Infect Dis 2004; 190:458.
26. de Giorgi V, Salvini C, Massi D, et al. Vulvar basal cell carcinoma: retrospective study and review of literature. Gynecol Oncol 2005; 97:192.
27. Piura B, Rabinovich A, Dgani R. Basal cell carcinoma of the vulva. J Surg Oncol 1999; 70:172.

28. Benedet JL, Miller DM, Ehlen TG, Bertrand MA. Basal cell carcinoma of the vulva: clinical features and treatment results in 28 patients. Obstet Gynecol 1997; 90:765.
29. Piura B, Egan M, Lopes A, Monaghan JM. Malignant melanoma of the vulva: a clinicopathologic study of 18 cases. J Surg Oncol 1992; 50:234.
30. Sugiyama VE, Chan JK, Shin JY, et al. Vulvar melanoma: a multivariable analysis of 644 patients. Obstet Gynecol 2007; 110:296.
31. Stang A, Streller B, Eisinger B, Jöckel KH. Population-based incidence rates of malignant melanoma of the vulva in Germany. Gynecol Oncol 2005; 96:216.
32. Chang AE, Karnell LH, Menck HR. The National Cancer Data Base report on cutaneous and noncutaneous melanoma: a summary of 84,836 cases from the past decade. The American College of Surgeons Commission on Cancer and the American Cancer Society. Cancer 1998; 83:1664.
33. Berek JS, Hacker NF. Berek & Hacker’s Gynecologic Oncology, 7th ed., Wolters Kluwer, 2021.
34. Johnson S, Renz M, Wheeler L, et al. Vulvar sarcoma outcomes by histologic subtype: a Surveillance, Epidemiology, and End Results (SEER) database review. Int J Gynecol Cancer 2020; 30:1118.
35. Han CH, Li X, Khanna N. Epithelioid sarcoma of the vulva and its clinical implication: A case report and review of the literature. Gynecol Oncol Rep 2016; 15:31.
36. Nasioudis D, Alevizakos M, Chapman-Davis E, et al. Rhabdomyosarcoma of the lower female genital tract: an analysis of 144 cases. Arch Gynecol Obstet 2017; 296:327.
37. Parker LP, Parker JR, Bodurka-Bevers D, et al. Paget's disease of the vulva: pathology, pattern of involvement, and prognosis. Gynecol Oncol 2000; 77:183.
38. Kibbi N, Owen JL, Worley B, et al. Anatomic Subtype Differences in Extramammary Paget Disease: A Meta-Analysis. JAMA Dermatol 2024; 160:417.
39. Kown BS, Ji YI, Jung MH, Kim YS. Total vaginectomy and radical vulvectomy for extension of extra-mammary Paget's disease. Eur J Gynaecol Oncol 2016; 37:861.
40. Fanning J, Lambert HC, Hale TM, et al. Paget's disease of the vulva: prevalence of associated vulvar adenocarcinoma, invasive Paget's disease, and recurrence after surgical excision. Am J Obstet Gynecol 1999; 180:24.
41. van der Linden M, Oonk MHM, van Doorn HC, et al. Vulvar Paget disease: A national retrospective cohort study. J Am Acad Dermatol 2019; 81:956.
42. Cai Y, Sheng W, Xiang L, et al. Primary extramammary Paget's disease of the vulva: the clinicopathological features and treatment outcomes in a series of 43 patients. Gynecol Oncol 2013; 129:412.

43. Jones IS, Crandon A, Sanday K. Paget's disease of the vulva: Diagnosis and follow-up key to management; a retrospective study of 50 cases from Queensland. Gynecol Oncol 2011; 122:42.
44. Feuer GA, Shevchuk M, Calanog A. Vulvar Paget's disease: the need to exclude an invasive lesion. Gynecol Oncol 1990; 38:81.
45. Kibbi N, Owen JL, Worley B, et al. Evidence-Based Clinical Practice Guidelines for Extramammary Paget Disease. JAMA Oncol 2022; 8:618.
46. DePasquale SE, McGuinness TB, Mangan CE, et al. Adenoid cystic carcinoma of Bartholin's gland: a review of the literature and report of a patient. Gynecol Oncol 1996; 61:122.
47. Visco AG, Del Priore G. Postmenopausal bartholin gland enlargement: a hospital-based cancer risk assessment. Obstet Gynecol 1996; 87:286.
48. Felix JC, Cote RJ, Kramer EE, et al. Carcinomas of Bartholin's gland. Histogenesis and the etiological role of human papillomavirus. Am J Pathol 1993; 142:925.
49. Copeland LJ, Sneige N, Gershenson DM, et al. Bartholin gland carcinoma. Obstet Gynecol 1986; 67:794.
50. Cardosi RJ, Speights A, Fiorica JV, et al. Bartholin's gland carcinoma: a 15-year experience. Gynecol Oncol 2001; 82:247.
51. Fine BA, Munoz AK, Litz CE, Gershenson DM. Primary medical management of recurrent aggressive angiomyxoma of the vulva with a gonadotropin-releasing hormone agonist. Gynecol Oncol 2001; 81:120.
52. Martelli H, Oberlin O, Rey A, et al. Conservative treatment for girls with nonmetastatic rhabdomyosarcoma of the genital tract: A report from the Study Committee of the International Society of Pediatric Oncology. J Clin Oncol 1999; 17:2117.
53. Shepherd V, Davidson EJ, Davies-Humphreys J. Extramammary Paget's disease. BJOG 2005; 112:273.
54. Seo T, Kitamura S, Yanagi T, et al. Prognostic Analysis of Patients With Extramammary Paget Disease Treated With Conservative Excision. Dermatol Surg 2023; 49:743.
55. Niikura H, Yoshida H, Ito K, et al. Paget's disease of the vulva: clinicopathologic study of type 1 cases treated at a single institution. Int J Gynecol Cancer 2006; 16:1212.
56. Tebes S, Cardosi R, Hoffman M. Paget's disease of the vulva. Am J Obstet Gynecol 2002; 187:281.
57. Hendi A, Brodland DG, Zitelli JA. Extramammary Paget's disease: surgical treatment with Mohs micrographic surgery. J Am Acad Dermatol 2004; 51:767.
58. Wagar MK, Zhang RC, Weisman P, et al. Fluorescein Mapping in Vulvar Paget Disease. Obstet Gynecol 2023; 141:608.

59. Zollo JD, Zeitouni NC. The Roswell Park Cancer Institute experience with extramammary Paget's disease. Br J Dermatol 2000; 142:59.
60. O'Connor WJ, Lim KK, Zalla MJ, et al. Comparison of mohs micrographic surgery and wide excision for extramammary Paget's disease. Dermatol Surg 2003; 29:723.
61. Bruce KH, Kilts TP, Lohman ME, et al. Mohs surgery for female genital Paget's disease: a prospective observational trial. Am J Obstet Gynecol 2023; 229:660.e1.
62. Yokoyama Y, Mabuchi M, Kawabata I, et al. Metastatic vulvar Paget's disease responding to combination chemotherapy: case report. Jpn J Clin Oncol 1990; 20:426.
63. Yamamoto R, Sakuragi N, Shirato H, et al. Radiotherapy with concurrent chemotherapy for vulvar adenocarcinoma associated with extramammary Paget's disease. Gynecol Oncol 2001; 80:267.
64. Huang GS, Juretzka M, Ciaravino G, et al. Liposomal doxorubicin for treatment of metastatic chemorefractory vulvar adenocarcinoma. Gynecol Oncol 2002; 87:313.
65. Hatch KD, Davis JR. Complete resolution of Paget disease of the vulva with imiquimod cream. J Low Genit Tract Dis 2008; 12:90.
66. Son SH, Lee JS, Kim YS, et al. The role of radiation therapy for the extramammary paget's disease of the vulva ; experience of 3 cases. Cancer Res Treat 2005; 37:365.
67. Sendagorta E, Herranz P, Feito M, et al. Successful treatment of three cases of primary extramammary Paget's disease of the vulva with Imiquimod--proposal of a therapeutic schedule. J Eur Acad Dermatol Venereol 2010; 24:490.
68. Hata M, Omura M, Koike I, et al. Role of radiotherapy as curative treatment of extramammary Paget's disease. Int J Radiat Oncol Biol Phys 2011; 80:47.
69. Pyle HJ, Goff HW, Nwachukwu CR, Mauskar MM. Treatment-refractory extramammary Paget disease responsive to radiotherapy. Am J Obstet Gynecol 2022; 226:852.
70. Brummer O, Stegner HE, Böhmer G, et al. HER-2/neu expression in Paget disease of the vulva and the female breast. Gynecol Oncol 2004; 95:336.
71. Richter CE, Hui P, Buza N, et al. HER-2/NEU overexpression in vulvar Paget disease: the Yale experience. J Clin Pathol 2010; 63:544.
72. Alsan CI, Vinh-Hung V, Eren F, Abacioğlu U. Adenoid cystic carcinoma of the Bartholin's gland: case report and systematic review of the literature. Eur J Gynaecol Oncol 2011; 32:567.
73. Kozakiewicz B, Dmoch-Gajzlerska E, Roszkowska-Purska K. Carcinomas and sarcomas of Bartholin gland. A report of nine cases and review of the literature. Eur J Gynaecol Oncol 2014; 35:243.
74. Balat O, Edwards CL, Delclos L. Advanced primary carcinoma of the Bartholin gland: report of 18 patients. Eur J Gynaecol Oncol 2001; 22:46.

75. Massad LS, De Geest K. Multimodality therapy for carcinoma of the Bartholin gland. Gynecol Oncol 1999; 75:305.
76. Yamada T, Yanagawa S, Iwai H, et al. High-dose-rate interstitial brachytherapy of Bartholin's gland: A case report. Gynecol Oncol 2000; 77:193.
77. López-Varela E, Oliva E, McIntyre JF, Fuller AF Jr. Primary treatment of Bartholin's gland carcinoma with radiation and chemoradiation: a report on ten consecutive cases. Int J Gynecol Cancer 2007; 17:661.
78. Downs LS, Ghosh K, Dusenbery KE, Cosin JA. Stage IV carcinoma of the Bartholin gland managed with primary chemoradiation. Gynecol Oncol 2002; 87:210.
79. Tanaka H, Umekawa T, Nagao K, et al. Adenocarcinoma of mammary-like glands in the vulva successfully treated by weekly paclitaxel. Int J Gynecol Cancer 2005; 15:568.

专题 3237 版本 47.0.zh-Hans.1.0

图表

WHO Classification of tumors of the vulva*¶

Epithelial tumors	
Squamous cell tumors and precursors	
Squamous intraepithelial lesions	
Low-grade squamous intraepithelial lesion	8077/0
High-grade squamous intraepithelial lesion	8077/2
Differentiated-type vulvar intraepithelial neoplasia	8071/2Δ
Squamous cell carcinoma	8070/3
Keratinizing	8071/3
Non-keratinizing	8072/3
Basaloid	8083/3
Warty	8051/3
Verrucous	8051/3
Basal cell carcinoma	8090/3
Benign squamous lesions	
Condyloma acuminatum	
Vestibular papilloma	8052/0
Seborrheic keratosis	
Keratoacanthoma	
Glandular tumors	
Paget disease	8542/3
Tumors arising from Bartholin and other specialized anogenital glands	
Bartholin gland carcinomas	
▪ Adenocarcinoma	8140/3
▪ Squamous cell carcinoma	8070/3
▪ Adenosquamous carcinoma	8560/3

Neuroectodermal tumors	
Ewing sarcoma	**9364/3**
Soft tissue tumors	
Benign tumors	
Lipoma	8850/0
Fibroepithelial stromal polyp	
Superficial angiomyxoma	8841/0Δ
Superficial myofibroblastoma	8825/0
Cellular angiofibroma	9160/0
Angiomyofibroblastoma	8826/0
Aggressive angiomyxoma	8841/0Δ
Leiomyoma	8890/0
Granular cell tumor	9580/0
Other benign tumors	
Malignant tumors	
Rhabdomyosarcoma	
Embryonal	8910/3
Alveolar	8920/3
Leiomyosarcoma	8890/3
Epithelioid sarcoma	8804/3
Alveolar soft part sarcoma	9581/3
Other sarcomas	
Liposarcoma	8850/3
Malignant peripheral nerve sheath tumor	9540/3
Kaposi sarcoma	9140/3
Fibrosarcoma	8810/3
Dermatofibrosarcoma protuberans	8832/1Δ
Melanocytic tumors	

▪ Adenoid cystic carcinoma	8200/3
▪ Transitional cell carcinoma	8120/3
Adenocarcinoma of mammary gland type	8500/3
Adenocarcinoma of Skene gland origin	8140/3
Phyllodes tumor, malignant	9020/3
Adenocarcinomas of other types	
Adenocarcinoma of sweat gland type	8140/3
Adenocarcinoma of intestinal type	8140/3
Benign tumors and cysts	
Papillary hidradenoma	8405/0
Mixed tumor	8940/0
Fibroadenoma	9010/0
Adenoma	8140/0
Adenomyoma	8932/0
Bartholin gland cyst	
Nodular Bartholin gland hyperplasia	
Other vestibular gland cysts	
Other cysts	
Neuroendocrine tumors	
High-grade neuroendocrine carcinoma	
Small cell neuroendocrine carcinoma	8041/3
Large cell neuroendocrine carcinoma	8013/3
Merkel cell tumor	8247/3

Melanocytic naevi	
Congenital melanocytic naevus	8761/0
Acquired melanocytic naevus	8720/0
Blue naevus	8780/0
Atypical melanocytic naevus of genital type	8720/0
Dysplastic melanocytic naevus	8727/0
Malignant melanoma	**8720/3**
Germ cell tumors	
Yolk sac tumor	**9071/3**
Lymphoid and myeloid tumors	
Lymphomas	
Myeloid neoplasms	
Secondary tumors	

WHO: World Health Organization; IARC: International Agency for Research on Cancer.

* The morphology codes are from the International Classification of Diseases for Oncology (ICD-O).[1] Behavior is coded /0 for benign tumors; /1 for unspecified, borderline, or uncertain behavior; /2 for carcinoma in situ and grade III intraepithelial neoplasia; and /3 for malignant tumors.

¶ The classification is modified from the previous WHO classification of tumors,[2] taking into account changes in our understanding of these lesions.

Δ These new codes were approved by the IARC/WHO Committee for ICD-O in 2013.

References:

1. *Fritz A, Percy C, Jack A, et al. International Classification of Diseases for Oncology (ICD-O), 3rd ed, World Health Organization, Geneva 2000.*
2. *Tavassoli FA, Devilee P. Pathology and Genetics of Tumours of the Breast and Female Genital Organs (IARC WHO Classification of Tumours). International Agency for Research on Cancer, Lyon 2003.*

Graphic 113829 Version 3.0

Vulvar cancer

Small vulvar carcinoma at the posterior fourchette.

Graphic 61663 Version 4.0

Vulvar cancer

Vulvar carcinoma in situ presenting as white or hyperpigmented lesion.

Graphic 71378 Version 1.0

Vulvar cancer

Vulvar carcinoma in situ before application of 5% acetic acid.

Graphic 50426 Version 3.0

Vulvar cancer

Exophytic squamous cell carcinoma involving the clitoris and right anterior labia.

Graphic 64265 Version 4.0

Vulvar squamous cell carcinoma: Fleshy, ulcerated lesion

Fleshy, ulcerated squamous cell carcinoma involving the left vulvar vestibule.

Graphic 130583 Version 2.0

Differential diagnosis of vulvar pruritus

Mild
Condylomata
Squamous cell carcinoma
Vulvar intraepithelial neoplasia
Syringoma
Angioma
Acrochordon
Polyp
Seborrheic keratosis
Perimenopausal atrophy
Irritants
Allergens
Sexually transmitted diseases
Moderate
Irritants
Allergens
Candidiasis
Seborrheic dermatitis
Vulvodynia
Severe
Lichen simplex chronicus
Lichen sclerosus
Lichen planus
Psoriasis
Pemphigus
Vulvodynia
Severe contact dermatitis
Severe candidiasis
Pediculosis pubis

Graphic 55449 Version 1.0

Vulvar squamous cell carcinoma and lichen sclerosus

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Graphic 80593 Version 5.0

Differential diagnosis of brown, blue, or black macules, papules, patches, an plaques on the vulva

Common	Less common	Rare
▪ Physiologic hyperpigmentation ▪ Postinflammatory hyperpigmentation ▪ Low-grade squamous intraepithelial lesions ▪ High-grade squamous intraepithelial lesions ▪ Melanocytic nevus ▪ Seborrheic keratosis ▪ Angiokeratoma ▪ Skin tags (acrochordons)	▪ Lentiginosis/vulvar melanosis ▪ Lichen planus ▪ Atypical melanocytic nevus ▪ Melanoma ▪ Varicosity	▪ Pigmented basal cell cancer ▪ Hidradenoma papilliferum ▪ Acanthosis nigricans

The prevalence categories refer to vulvar manifestations of the listed diseases. The relative frequency of each may vary based on the patient population, geography, and type of clinical practice (eg, gynecology, dermatology, or internal medicine).

Graphic 95978 Version 6.0

Vulvar lichen sclerosus and squamous cell carcinoma

Lichen sclerosus with a classic butterfly distribution and early invasive cancer on the left.

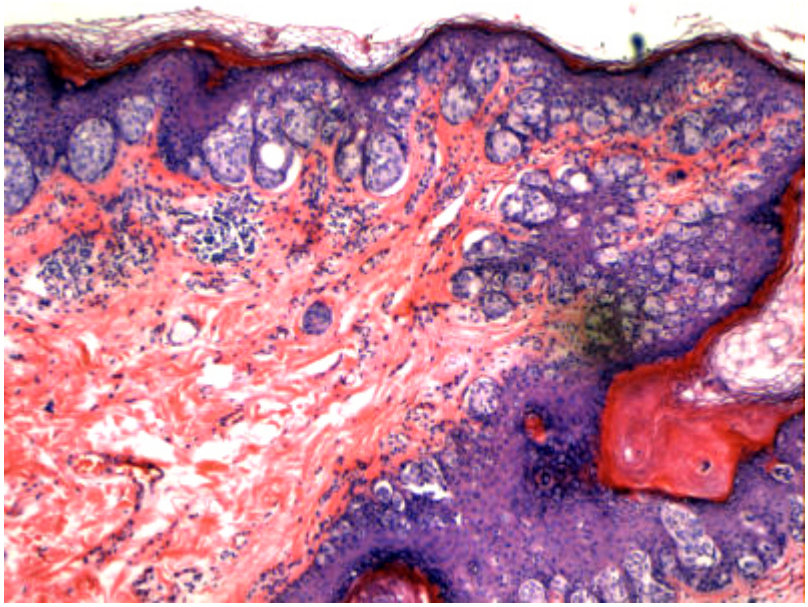
Graphic 130582 Version 2.0

Extensive Paget disease of the vulva

The lesion on the right posterior aspect of the vulva has a weeping, eczematoid appearance; there is extension onto the inner thigh. Biopsies showed no evidence of invasive cancer.

Graphic 130581 Version 2.0

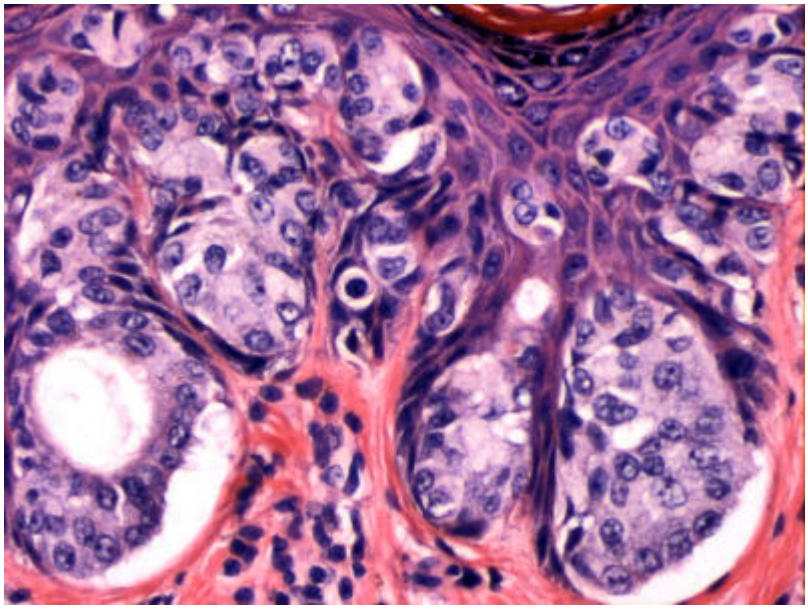
Extramammary Paget disease of the vulva



Courtesy of William J Mann, Jr, MD.

Graphic 62814 Version 1.0

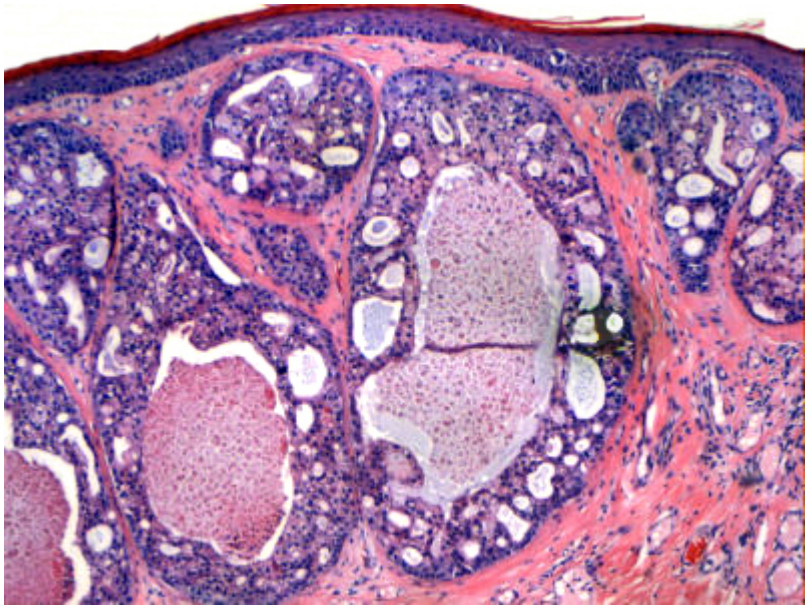
Extramammary Paget disease of the vulva-2



Courtesy of William J Mann, Jr, MD.

Graphic 77680 Version 1.0

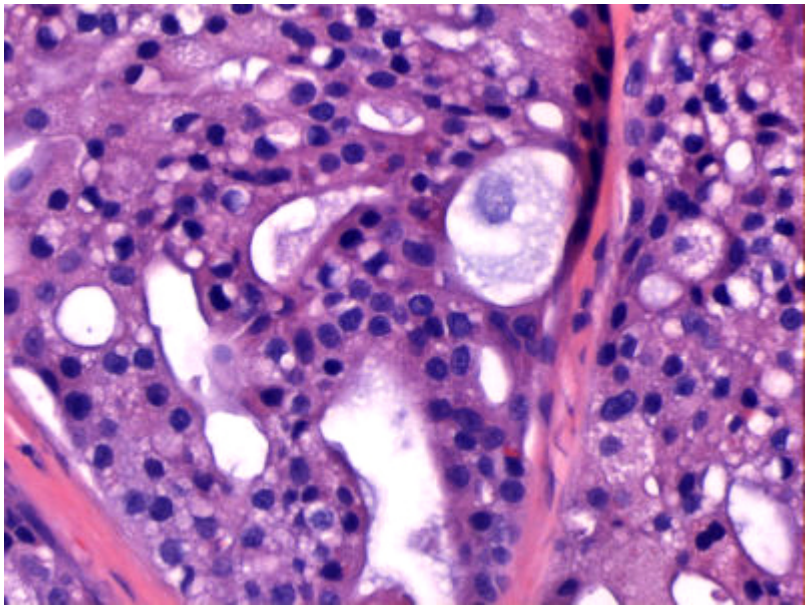
Extramammary Paget disease of the vulva with adenocarcinoma



Courtesy of William J Mann, Jr, MD.

Graphic 69564 Version 1.0

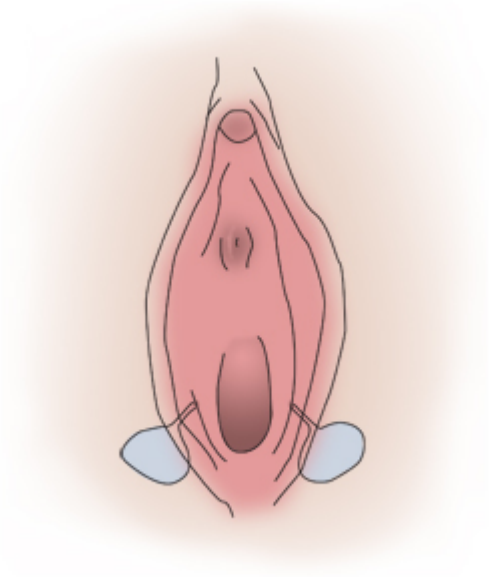
Extramammary Paget disease of the vulva with adenocarcinoma-2



Courtesy of William J Mann, Jr, MD.

Graphic 81965 Version 1.0

Location of the Bartholin glands and ducts



Each Bartholin gland is approximately 0.5 centimeter (cm) in size and drains into a duct 2.5 cm long. The ducts emerge onto the vestibule, one at each side of the vaginal orifice, in the groove (superficial perineal pouch) between the hymenal ring and the labia minora.

Graphic 66162 Version 2.0

Contributor Disclosures

Jonathan S Berek, MD, MMSc Grant/Research/Clinical Trial Support: Eisai [Ovarian cancer]; Immunogen [Ovarian cancer]; Karyopharm [Endometrial cancer]. Consultant/Advisory Boards: Merck [Ovarian cancer]. All of the relevant financial relationships listed have been mitigated. **Amer Karam, MD** Speaker's Bureau: Astra Zeneca [Gynecologic malignancies]. All of the relevant financial relationships listed have been mitigated. **Barbara Goff, MD** No relevant financial relationship(s) with ineligible companies to disclose. **Don S Dizon, MD, FACP** Equity Ownership/Stock Options: Doximity [Social media]; Midi [Social media community app]. Grant/Research/Clinical Trial Support: Bristol-Myers Squibb [Ovarian cancer, cervical cancer]. Consultant/Advisory Boards: AstraZeneca [Ovarian cancer, endometrial cancer]; Clovis Oncology [Ovarian cancer]; Glaxo Smith Kline [Endometrial cancer]; Kronos Biotech [Disparities]; Midi [Women's health]; Pfizer [Social media]. Other Financial Interest: Global Cancer Institute [Gynecologic oncology]. All of the relevant financial relationships listed have been mitigated. **Alana Chakrabarti, MD** No relevant financial relationship(s) with ineligible companies to disclose.

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