Advances in Clinical Medicine 临床医学进展, 2024, 14(2), 2575-2582
Published Online February 2024 in Hans. https://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2024.142363

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外阴癌诊治进展

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收稿日期：2024年1月5日；录用日期：2024年1月31日；发布日期：2024年2月6日

摘 要

外阴癌是一种较为少见的妇科恶性肿瘤，仅占女性生殖系统恶性肿瘤的2%~5%，在绝经后妇女较为多见。但近些年来，外阴癌的发病率不断升高。外阴上皮内病变(vulvar squamous intraepithelial lesions, VSIL)是外阴癌的癌前病变，在年轻女性中发病率也有所提升。绝大多数外阴癌患者的组织学分型是外阴鳞状细胞癌(vulvar squamous carcinoma, VSCC)。外阴癌患者临床常表现为外阴瘙痒、溃疡，通常还可伴有疼痛、出血、排尿困难和阴道排液等。其治疗方式主要根据组织类型及手术分期决定，为手术结合放化疗综合治疗。

关键词

外阴癌，人乳头状瘤病毒，外阴上皮内瘤变，治疗，预后

Progress of Diagnosis and Treatment of Vulvar Cancer

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Received: Jan. 5th, 2024; accepted: Jan. 31st, 2024; published: Feb. 6th, 2024

Abstract

Vulvar cancer is a relatively rare gynecological malignant tumor, accounting for only 2%~5% of the malignant tumors of the female reproductive system, and is more common in postmenopausal women. However, in recent years, the incidence of vulvar cancer has been increasing. Vulvar squamous

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文章引用: 吐鲁娜依·地里木拉提, 古扎丽努尔·阿不力孜. 外阴癌诊治进展[J]. 临床医学进展, 2024, 14(2): 2575-2582. DOI: 10.12677/acm.2024.142363

intraepithelial lesions (VSIL), precancerous lesions of vulvar cancer, are also increasing in younger women. The tissue type of the vast majority of vulvar cancer patients is vulvar squamous carcinoma (VSCC). Vulvar cancer patients are often clinical manifestations of vulvar pruritus, ulcers, often accompanied by pain, bleeding, dysuria and vaginal drainage. Its treatment is mainly determined by the type of tissue and the stage of surgery, which is combined with radiotherapy and chemotherapy.

Keywords

Vulvar Cancer, Human Papilloma Virus, Vulvar Intraepithelial Neoplasia, Treatment, Prognosis

1. 引言

外阴癌被认为是一种罕见的妇科恶性肿瘤。国际癌症研究机构(IARC)估计，每年约有 45,000 例外阴癌新诊断病例，这种肿瘤每年造成约有 17,000 人死亡[1] [2]，因大多数早期外阴癌患者临床症状不明显，且无明确的外阴癌筛查方式，导致许多患者误诊漏诊未得到及时诊治，本文将通过外阴癌发病相关因素、发病机制及诊疗方法来说明当前外阴癌诊治进展。

2. 发病相关因素

2.1. 人乳头状瘤病毒(Human Papilloma Virus, HPV)

HPV 是一种小分子量双链的 DNA 病毒，可通过入侵生殖道鳞状上皮细胞，导致细胞分化失调，引起局部上皮增生，甚至癌变[3] [4]。HPV 感染占全球所有新发癌症病例的 4.5%，占所有感染相关癌症的 29.5% [5]。约 40%的外阴癌患者可检测出 HPV-DNA [6] [7]，主要以 HPV16、18、31、33 型多见。年轻女性常见疣状/基底细胞样鳞癌，是由高危型 HPV(超过 50%为 16 型)持续感染导致[8]。研究表明，高危型的 HPV (16、18 型等)的致病机制主要与 E6、E7 这两个基因有关。HPV E6 蛋白与细胞内肿瘤抑制物 p53 结合，使 p53 快速降解，导致细胞周期失控，从而导致外阴癌的发生。其效应等同于 p53 突变[9]。此外，E6 蛋白致病机制还具有 p53 非依赖途径[10] [11]，高危型 HPV 的 E6 可以直接与血管内皮生长因子作用，促进外阴癌的发生发展。HPV 的 E7 蛋白的致病机制是通过使细胞染色体复制异常来完成的。HPV 感染持续时间越长，其 E6 和 E7 癌蛋白更多干扰细胞周期的调节机制从而导致外阴癌的发生[12]。

2.2. 单纯疱疹病毒(Herpes Simplex Virus, HSV)感染

HSV 根据抗原可分为 HSV I 型和 HSV II 型，其中外阴癌患者的 HSV II 阳性率以及生殖系统疱疹感染率较高[13]。研究表明，HSV 可能是独立致癌因素，HSV 可通过 T 抗原进入细胞核，生成 DNA 病毒，致使基因突变[14] [15]。当人体感染 HSV 病毒，会引起集体特异性免疫，但大多数时候无法被彻底清除，从而潜伏在机体中，当宿主免疫力低下时再次转为增殖性感染从而再次损害机体，可能会成为生殖系统肿瘤的辅助致病因素[16]。

2.3. 自身免疫障碍

机体免疫力低下及免疫功能损坏可能导致肿瘤的发生[17]。据当前研究报道肾移植者患外阴癌的风险

比正常女性高 100 倍[18]。感染 HIV 的妇女外阴上皮内病变的风险是未感染者的 29 倍，并有恶变的可能。HIV 阳性妇女发生外阴癌的风险是 HIV 阴性妇女的 6 倍[19]。

2.4. 性传播疾病

研究提示外阴癌的发生与性传播疾病病史如尖锐湿疣、淋病、梅毒、沙眼衣原体感染、单纯疱疹病毒 II 型感染等有关。有淋病史女性患外阴癌的相对危险性是无淋病患者的 5 倍，有尖锐湿疣的相对危险性则为 17.3 倍[20] [21]。

2.5. 外阴白色病变

属于非 HPV 依赖的外阴癌致病因素。外阴白色病变包括外阴硬化性苔藓(VLS)外阴鳞状上皮增生(VSH)及其他外阴皮肤和黏膜的病变。VLS 病人有 4%~6%可能演变为外阴癌，建议有硬化苔癣的患者应该长期随访[22] [23]。外阴白色病变病因和发病机制至今尚不明确。可能与免疫因素、炎症感染、细胞凋亡与增殖、局部环境代谢紊乱及遗传因素有关[22]。因其病因不明，外阴硬化性苔藓暂无明确的治疗指南。治疗上主要是避免(如局部刺激引起的创伤、封闭潮湿的环境)等诱发因素，为缓解其外阴瘙痒等临床症状，可局部使用高效糖皮质激素[24] [25]，尽量避免瘢痕形成。

2.6. 其他相关因素

外阴癌还可能与种族、吸烟、基础疾病、工作环境等有关[26]。研究表明，吸烟者发生外阴原位癌和浸润癌的相对危险为 6.4。HPV16 血清阳性的吸烟者相比较不吸烟的 HPV 阳性者，其与外阴癌比值比是 18.8，说明吸烟是外阴癌的危险因素[27]。

3. 发病机制

外阴病变的命名在近年来不断更改，2014 年世界卫生组织(WHO)女性生殖器肿瘤分类将外阴癌前病变被分成 3 种亚型：低级别鳞状上皮内病变(vulvar low-grade squamous intraepithelial lesions, VLSIL)，高级别鳞状上皮内病变(vulvar high-grade squamous intraepithelial lesions, VHSIL)和分化型外阴鳞状上皮内瘤变(differentiated vulvar intraepithelial neoplasia, dVIN)。外阴鳞状细胞癌的发展有两种不同的病因途径。第一个途径是 HPV 阳性外阴癌相关途径。HPV 依赖的 VSCC 与其他与 HPV 相关的癌症具有相同的流行病学特征。其高危因素是吸烟和免疫抑制，而 VSIL 是其癌前病变。LSIL 与高低危型 HPV 都相关，其病变常自行退化，很少发展为浸润癌。常见于年轻女性，HSIL 常发生于绝经前女性，多与高危型 HPV(常见 16 型)有关，发展为浸润癌概率很高。常会演变为疣状或基底细胞样鳞癌[28] [29]。目前研究 VSIL 转化为外阴癌的机制可能与血管生长因子[30]、细胞周期相关蛋白(pRB2/pl30)表达、微血管密度(MVD)增高[31]相关。第二个途径是 hpv 阴性外阴癌相关途径，常发生在老年女性，这类群体通常有外阴慢性皮肤病、长期硬化性苔藓(lichen sclerosus, LS)或自身免疫性疾病背景。此类型常演变为 dVIN。dVIN 的发病因素及生物学行为等与 LSIL、HSIL 不同，其发展为浸润癌概率极高，预后较差，复发率高[32]。

4. 外阴癌诊治

4.1. 外阴癌的诊断

外阴恶性肿瘤金标准是对可疑病灶活检得出病理诊断，外阴恶性肿瘤的组织学类型在 2014 年被 WHO 分类 60 余种，绝大多数的外阴恶性肿瘤患者是鳞状细胞癌。其次是恶性黑色素瘤。还包括外阴前庭大腺癌、外阴 Paget 病、外阴基底细胞癌等[33]。80%外阴鳞状细胞癌病变分布在大阴唇及小阴唇，其余 20%分别位于阴蒂和阴道前庭。肿瘤病灶往往分布在单侧，只有少数分布于双侧，极少数为多灶性浸

润。外阴恶性肿瘤早期临床症状最常见为外阴瘙痒，局部肿块或溃疡，也可能出现阴道异常排液[34]。因此外阴癌症早期常被当为炎症性疾病，易误诊、漏诊。很多患者由于有长时间的外阴硬化性苔藓或 HSIL 的病史而长期存在外阴异常症状。

外阴癌的诊断主要靠临床表现与组织学检查进行评估，妇科检查需注意病灶范围、程度、大小、质地、色素改变、活动度、是否累及周围器官及双侧腹股沟区是否有肿大淋巴结，并检查阴道、宫颈以排除是否有其他部位肿瘤。任何可疑病灶都需活检进行病理诊断排除浸润癌。可在局麻下活检。由于当前临床上没有明确的外阴癌筛查方法以及在妇科检查时未能认真检查外生殖器，以及临床上滥用抗真菌药物及激素类药物，从患者发现异常到明确诊断的时间延误平均 15 个月[35]。如果发现可疑区域，可进行组织学检查，在使用皮肤活检打孔器时尽量取至表皮基底层。多灶性病变诊断时需要进行多次多点穿刺活检[36]。其他检查还包括外阴细胞学检查，HIV 检测，影像学检查胸片、CT 等。对于早期肿瘤，可使用盆腔和腹股沟 CT 或 MRI 扫描协助判断相应部位是否有肿大淋巴结以及是否有转移灶或是否侵犯骨质。有利于制定后续治疗方案。PET CT 则是更高效地评估及检测到病灶是否有腹股沟淋巴结转移，可帮助制定肿瘤部位及淋巴结切除方案以达到最佳的手术切除范围。PET-CT 还可用于准备手术的同时合并考虑有转移的大块型病灶或复发患者[37]。

4.2. 外阴癌的治疗

外阴癌的治疗取决于疾病的分期。手术方式取决于肿瘤的大小和位置、组织学和细胞学分级、浸润深度，特别是淋巴结转移，这些也与疾病预后息息相关。外阴癌的治疗应个体化，尽量采用最保守的手术方式来完成最好的治疗效果。且选择一种效率更高、并发症发生率更低的治疗手段。

4.2.1. 微浸润型外阴癌(IA 期)

IA 期是指直径 ≤ 2.0 cm，浸润深度 ≤ 1.0 mm 的单个病灶。可作足够范围的局部切除术治疗，切除范围需超出病灶范围 1 cm。保证切缘阴性因这种情况下局部病灶复发和淋巴结转移较为少见，故常规一般不清扫淋巴结[38]。

4.2.2. 早期外阴癌

肿瘤病灶仅局限于外阴，需经临床检查和影像学检查评估排除淋巴结转移时可诊断为早期外阴癌。早期外阴癌的手术治疗方案是局部广泛切除术。须保证 2 cm 的手术切缘已达到至少 8 mm 以上的病理阴性切缘。单侧小病灶(病灶直径小于 4 cm 及距外阴中线部位 ≥ 2 cm)且同侧淋巴结阴性患者不需要切除对侧腹股沟淋巴结。有 IB 期或 II 期的外阴癌患者都需行腹股沟淋巴结切除术[39]。肿瘤病灶距离中线距离 < 2 cm，或已超过中线的，也应行双侧腹股沟淋巴结切除术。肿瘤病灶累及小阴唇及单侧病灶直径 > 4 cm 或单侧腹股沟淋巴结阳性的患者，更应该行双侧腹股沟淋巴结切除术[40] [41] [42]。早期外阴癌术式与以往术式相比在保证足够范围的切除降低复发率的同时，更好地保证周围组织的完整性，降低手术并发症如感染、坏死，且有效改善年轻女性对外阴外形满意度及生活质量[43] [44]。

前哨淋巴结技术在早期外阴癌患者中的应用逐渐增加，理论上外阴癌肿瘤浸润深度超过 1 mm 就可能出现腹股沟淋巴结转移，而前哨淋巴结(sentinellymph node)应最先受累，早期外阴癌患者腹股沟淋巴结转移率不足 30%，也就是说相当 70%的病人做了不必要的腹股沟淋巴结清扫术，而前哨淋巴结技术则大大减少了这种可能性，避免了常规双侧淋巴结切除术的并发症(发生下肢淋巴水肿的风险约 30%~70%) [45] [46]，缩短了术后恢复的时间，且不会明显增加复发风险[47]。腹股沟转移淋巴结的数目及大小及是否存在包膜外扩散十分影响预后，无淋巴结包膜外扩散的患者只行腹股沟淋巴结切除术的预后良好，无需额外进行放射治疗。

一旦在前哨淋巴结活检时发现有淋巴结转移，该患者必须进行腹股沟淋巴结切除术，术后还需补充放射治疗。大部分患者的体外放射治疗(external beam radiotherapy, EBRT)放射部位应包括腹股沟及髂外及髂内淋巴结区[48]。若发现广泛的腹股沟淋巴结受累或考虑可疑的盆腔淋巴结转移，放射治疗时须扩大放疗野上界[49]。

4.2.3. 晚期外阴癌

晚期外阴癌是指原发病灶范围超出外阴和(或)有大块腹股沟淋巴结阳性者。晚期外阴癌的诊治需要个体化及多学科综合治疗。治疗方案及术式根据淋巴结受累情况而决定，若怀疑腹股沟淋巴结转移，需行淋巴结活检明确诊断，结合体格检查或影像学材料若均不提示淋巴结转移，则行双侧腹股沟淋巴结切除术。若术后病理提示淋巴结阳性，则需行腹股沟及盆腔部位的辅助放疗。若术后淋巴结均阴性，则无需术后放疗。若腹股沟淋巴结出现溃疡或固定，应先活检确诊后再行放化疗。在放疗未能完全改善病情的情况下，则可在放疗后行腹股沟淋巴结切除。放疗前也可以新辅助化疗以缩小淋巴结。手术最理想结果是未损伤周围组织器官且切除肿瘤切缘阴性，手术可迅速缓解溃疡、疼痛、排液等症状。病灶距离手术切缘过近的患者可从术后辅助放疗，术后放疗后的残余病灶也有助于降低复发率和提高生存率。对于不适合手术的患者，放疗则为最好的治疗选择[50]。有 15%~35%的外阴癌患者可能会复发，通常由复发的部位、患者的一般情况、分期检查的结果来决定复发性外阴癌治疗方案。可选择的治疗包括手术、放(化)疗、新辅助或姑息性化疗、靶向治疗或最佳支持治疗[51]。药物化疗常与放射治疗一起成为外阴癌术后补充治疗，常用的药品有顺铂、氟尿嘧啶等等。

4.3. 其他类型外阴恶性肿瘤

4.3.1. 外阴恶性黑色素瘤

外阴黑色素瘤是继 VSCC 之后第二常见的外阴癌，虽然外阴仅占体表面积的 0.7%；女性患者中有2%的黑色素瘤发生在外阴[52]。外阴恶性黑色素瘤常由外阴色素痣恶变而来，早期肿瘤表现为棕黑色的凸起结节，晚期可发展为溃疡，在进行诊断性组织活检时可将病灶完整切除，切缘距离肿瘤边缘至少 1 cm。其复发率高，腹股沟淋巴结转移常见[53]。

4.3.2. 外阴前庭大腺癌

外阴前庭大腺癌占所有外阴恶性肿瘤的 7.7% [54]，病因尚不清楚，可能与单纯疱疹病毒 2 型、人乳头瘤状病毒和巨细胞病毒等致前庭大腺囊肿与前庭大腺癌的发生可能有关。治疗暂不明确，可行根治性外阴切除或根治性部分外阴切除术及单侧或双侧腹股沟淋巴结切除术。

4.3.3. 外阴 Paget 病

是一种罕见的妇科恶性肿瘤，仅占外阴恶性肿瘤的 1%~2% [55]，本病病程长，发展缓慢，大多数病人临床症状不明显，病灶常呈多灶状。通常发生在 53~75 岁的绝经后妇女[56]。手术治疗易合并并发症，且复发率较高。

4.3.4. 外阴基底细胞癌

外阴基底细胞癌是一种较罕见的外阴恶性肿瘤，占外阴恶性肿瘤的 2%~4% [57]。其症状有外阴色素沉着，瘙痒、溃疡等。病程长，发展慢，较难转移，因此该病预后良好，以大阴唇局部浸润性生长为主，以手术治疗为主[58] [59]。

5. 随访

与其他妇科恶性肿瘤治疗后随访原则相同。治疗后前 2 年每 3~6 个月随访 1 次，第 3~5 年每 6~12

个月随访 1 次，以后每年随访 1 次。随访时建议完善宫颈/阴道细胞学筛查及 HPV 检测，若症状或临床检查怀疑复发，需结合影像学及肿瘤标志物检查，必要时行活组织病理学检查明确。

综上，外阴恶性肿瘤的发病率一直在增加，特别是在 hpv 相关的外阴恶性肿瘤。许多外阴恶性肿瘤早期因被误诊为炎症，病情加重，预后不良。早期治疗和干预通常会更有利得预后。手术是外阴癌的主要治疗方法。在制定治疗方案时宜讲究个体化治疗。在尽可能保守的情况下，采用最高效、并发症最低的治疗方式，改善患者的预后及生活质量。

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