Vulval cancer and vulval intraepithelial neoplasia

Vulval cancer is a very rare disease and, on average, a GP will only see a new case once every seven years. 85% of cancers of the vulva are squamous and the remaining are of various histological types, including melanomas. The labium majorum is the most common site of involvement and accounts for about 50% of cases. The labium minorum accounts for about 20% of cases. The clitoris and Bartholin's glands are less frequently involved. Usually it spreads slowly, locally and metastasises to groin nodes and from there to pelvic nodes.

How common is vulval cancer? (Epidemiology) [1]

- In females in the UK, vulval cancer is not among the 20 most common cancers, with around 1,400 new cases every year (2016-2018). However, vulval cancer accounts for less than 1% of all new cancer cases in females in the UK (2016-2018).
- Vulval cancer incidence is strongly related to age, with the highest incidence rates being in older women. In the UK nearly half of all cases are diagnosed in women aged 75 years and over, and nearly three quarters are in those aged 60 years and over. Incidence rates for vulval cancer in the UK are highest in females aged 90+ (2016-2018).
- Vulval cancer incidence rates in England in females are 74% higher in the most deprived quintile compared with the least (2013-2017).
- The incidence in women aged 40-49 years has doubled over the period of three decades. This is thought to be due to the effect of increasing human papillomavirus (HPV) infection.

- 90% of vulval cancers are due to squamous cell carcinoma (SCC). The others comprise basal cell carcinomas, adenocarcinomas, sarcomas and melanomas.

Risk factors

- Vulval intraepithelial neoplasia (VIN) is considered a pre-malignant state.
- Lichen sclerosus - risk of developing invasive disease is around 4%. This risk may not be reduced by treatment.[2]
- HPV infection - seen in younger women and may be multifocal.
- Paget's disease of the vulva (adenocarcinoma in situ) and melanoma in situ are both pre-invasive conditions.[3] These are both rare, but they have a significant risk of invasion.

Vulval intraepithelial neoplasia

- VIN is considered a pre-malignant state. It can occur by means of cell transformation in already existing vulval disorders such as lichen sclerosus and squamous cell hyperplasia or it can occur independently.[4]
- Screening tests are not available for VIN.
- VIN is a histological diagnosis and therefore requires a biopsy.

- There are two types of VIN:[4]
    - Usual type:
        - Higher incidence in younger women.
        - HPV-related
        - Women with usual-type VIN are at a higher risk of developing another HPV-related malignancy of the anogenital tract.
        - Current prophylactic HPV vaccines offer protection against usual-type VIN and related invasive carcinoma.
    - Differentiated type:
        - More common in older patients with chronic dermatological conditions.
        - Greater invasive potential and shorter time between diagnosis and SCC than usual-type VIN.
        - Not HPV-related.
- Most women with VIN have pruritus, but some are asymptomatic. The lesions may be white, grey, red or raised.
- The diagnosis of VIN is carried out by identifying a lesion by visual inspection and confirming by performing a biopsy.[5]
- Management: biopsy is performed before laser therapy, to make sure that a lesion does not contain invasive cancer.
- High rates of recurrence are associated with smoking, larger lesion size, and positive margins.[6]
- Conventional treatment is wide local excision.[7] Because of the close association of VIN with HPV infection, lifelong follow-up is required to watch for recurrence.

- Topical imiquimod appears to be a safe and effective treatment for high-grade VIN, even though local side-effects may necessitate dose reductions. However, longer-term follow-up data are needed to corroborate the limited evidence that response to treatment is sustained, and to assess any effect on progression to vulval cancer. Available evidence suggests that topical cidofovir may be a good alternative to imiquimod.[8]
- As some lesions spontaneously regress, some women have no active treatment. This may be the best policy for partial-thickness VIN. However, there is a risk of progression and women should be made aware of this.[9]

Vulval cancer symptoms

- Vulval cancer may present with a vulval lump, vulval bleeding due to ulceration, pruritus or pain. Presentation is often delayed.[10]
- There should be a high index of suspicion for abnormal lesions on the vulva, including 'warts' in the postmenopausal woman.
- 75% of all growths are primarily on the labia.
- Vulval cancers may sometimes be diagnosed incidentally - for example, when examining a woman for another procedure (eg, colposcopy).
- The pattern of spread is influenced by the histology. Well-differentiated lesions tend to spread along the surface with minimal invasion, while anaplastic lesions are more likely to be deeply invasive.
- Spread beyond the vulva is either to adjacent organs such as the vagina, urethra and anus, or via the lymphatics to the inguinal and femoral lymph nodes, followed by the deep pelvic nodes.
- Approximately 30% of women with operable disease have nodal spread.

Investigations

- The diagnosis of vulval cancer is made by examination and biopsy.

- Other investigations such as cystoscopy, proctoscopy, CXR and MRI scans are used for staging purposes.

Editor's note
Dr Krishna Vakharia, 16th October 2023 **Suspected cancer: recognition and referral** [11] The National Institute for Health and Care Excellence (NICE) has recommended that a person should receive a diagnosis or ruling out of cancer within 28 days of being referred urgently by their GP for suspected cancer.

Differential diagnosis

- Lichen planus.
- Ulcers: for example, herpes, Crohn's disease, Behçet's disease, syphilis.
- Dermatitis.
- Fungal infection.
- Other causes of swellings of the vulva include boils, sebaceous cysts, Bartholin's cyst or abscess and urethral caruncle.

Staging [12]

Stages are defined by the Fédération Intérnationale de Gynécologie et d'Obstétrique (FIGO):

Stage I: tumour confined to the vulva:

- IA lesions: ≤2 cm in size, confined to the vulva or perineum and with stromal invasion up to 1.0 mm, no nodal metastasis.
- IB lesions: >2 cm in size, or with stromal invasion >1.0 mm, confined to the vulva or perineum, with negative nodes.

Stage II: tumour of any size with extension to adjacent perineal structures (1/3 lower urethra, 1/3 lower vagina, anus) with negative nodes.

Stage III: tumour of any size with or without extension to adjacent perineal structures (1/3 lower urethra, 1/3 lower vagina, anus) with positive inguino-femoral lymph nodes:

- IIIA (i): tumour of any size with extension to upper part of adjacent perineal structures, or with any number of non-fixed, non-ulcerated lymph node, or (ii) tumour 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 (i): regional (inguinal and/or femoral) lymph node metastases >5 mm.
- IIIC: regional lymph node metastases with extracapsular spread.

Stage IV: tumour invades other regional (2/3 upper urethra, 2/3 upper vagina), or distant structures:

- IVA: disease fixed to pelvic bone, or fixed or ulcerated regional lymph node metastases.
- IVB: any distant metastasis.

When to refer

- The following women should be referred urgently (two-week referral): [11]
    - Women presenting with an unexplained vaginal lump.
    - Women with unexplained vulval bleeding or ulceration.
- For women who present with vulval pruritus or pain and in whom vulval cancer is not immediately suspected, a period of 'treat, watch and wait' is reasonable. However, those women with persistent symptoms should be referred for a gynaecological opinion; this may be urgent or routine depending on the degree of patient/doctor concern about the possibility of cancer. [10]

NB: women with uncomplicated lichen sclerosus do not require routine hospital-based follow-up, but should be informed of the risks of invasion. [10]

Vulval cancer treatment and management

- Standard treatment in vulval cancer is surgery.
- The standard radical mutilating surgery for the treatment of invasive vulval carcinoma is now being replaced by a conservative and individualised approach.[13] Factors such as tumour size, location, medical fitness and the wishes of the patient will all influence management.
- Primary vulval cancer is usually treated with radical/wide local resection. In cases of other suspicious lesion or multifocal disease, radical vulvectomy is usually performed.[14]
- There are significant morbidity and psychosexual problems following groin node dissection.[15]
- Reconstructive surgery is often undertaken.
- Radiotherapy, with or without chemotherapy, is increasingly used in the management of advanced vulval cancer.
- The greatest single factor in reducing mortality from vulval cancer is appropriate groin node dissection.[10] However, groin node dissection should be omitted if the patient has stage Ia disease, as the incidence of lymph node metastases is negligible.
- Sentinel lymph node biopsy (SLNB) is increasingly being shown to be of value in the detection of sentinel nodes and can reduce the need for groin node dissection by 70% in women with early vulval cancer.[16] This technique is associated with significantly less postoperative morbidity when compared with groin node dissection.
- It has been suggested that women should make an informed choice between the slightly higher groin recurrence rates of SLNB and the greater morbidity of groin node dissection.[17]
- Complications from surgery remain high and include:[18] :
    - Wound breakdown and infection.
    - Introital stenosis.
    - Urinary and/or faecal incontinence.
    - Lymphoedema.

There is increasing evidence for the safety and efficacy of 5% imiquimod for the treatment of Paget's disease of the vulva.[3]

Prognosis[1]

- 86.1% of women diagnosed with vulval cancer in England survive their disease for one year or more (2013-2017).
- 67.1% of women diagnosed with vulval cancer in England survive their disease for five years or more (2013-2017).
- Vaginal and vulva cancer survival in England are highest for women diagnosed aged under 50 years (2009-2013).
- More than 80% of women in England diagnosed with vaginal or vulval cancer aged 15-49 survive their disease for five years or more, compared with almost 60% of women diagnosed aged 70-89 (2009-2013).
- When diagnosed at its earliest stage, 96% of people with vulval cancer will survive their disease for one year or more, compared with 43% of people when the disease is diagnosed at the latest stage.
- Survival from vulval cancer has improved and mortality has decreased since 1990.[19]
- Lymph node metastasis is the most important prognostic factor for recurrence and survival in vulval carcinoma.[20]

Prevention

High-risk HPV types 16 and 18 are strongly implicated in anal/genital cancers (penis, vagina and vulva, anus). See also the separate article on Human Papillomavirus (HPV) Vaccination.

References

1. Vulval cancer statistics; Cancer Research UK
2. Green C, Guest J, Ngu W; Long-term follow-up of women with genital lichen sclerosus. Menopause Int. 2013 Feb 15.

3. Edey KA, Allan E, Murdoch JB, et al; Interventions for the treatment of Paget's disease of the vulva. Cochrane Database Syst Rev. 2019 Jun 5;6:CD009245. doi: 10.1002/14651858.CD009245.pub3.
4. Reyes MC, Cooper K; An update on vulvar intraepithelial neoplasia: terminology and a practical approach to diagnosis. J Clin Pathol. 2014 Apr;67(4):290-4. doi: 10.1136/jclinpath-2013-202117. Epub 2014 Jan 7.
5. Preti M, Scurry J, Marchitelli CE, et al; Vulvar intraepithelial neoplasia. Best Pract Res Clin Obstet Gynaecol. 2014 Oct;28(7):1051-62. doi: 10.1016/j.bpobgyn.2014.07.010. Epub 2014 Jul 18.
6. Wallbillich JJ, Rhodes HE, Milbourne AM, et al; Vulvar intraepithelial neoplasia (VIN 2/3): comparing clinical outcomes and evaluating risk factors for recurrence. Gynecol Oncol. 2012 Nov;127(2):312-5. doi: 10.1016/j.ygyno.2012.07.118. Epub 2012 Aug 4.
7. Kaushik S, Pepas L, Nordin A, et al; Surgical interventions for high-grade vulval intraepithelial neoplasia. Cochrane Database Syst Rev. 2014 Mar 4;3:CD007928. doi: 10.1002/14651858.CD007928.pub3.
8. Pepas L, Kaushik S, Nordin A, et al; Medical interventions for high-grade vulval intraepithelial neoplasia. Cochrane Database Syst Rev. 2015 Aug 18;2015(8):CD007924. doi: 10.1002/14651858.CD007924.pub3.
9. UK National Guideline on the Management of Vulval Conditions; British Association for Sexual Health and HIV (2014)
10. Guidelines for the Diagnosis and Management of Vulval Carcinoma; Royal College of Obstetricians and Gynaecologists (updated May 2022)
11. Suspected cancer: recognition and referral; NICE guideline (2015 - last updated October 2023)
12. 2021 FIGO Staging System for Vulvar Cancer, summary and comparison with 2009 FIGO Staging System; British Association of Gynaecological Pathologists.
13. Micheletti L, Preti M; Surgery of the vulva in vulvar cancer. Best Pract Res Clin Obstet Gynaecol. 2014 Oct;28(7):1074-87. doi: 10.1016/j.bpobgyn.2014.07.011. Epub 2014 Jul 22.
14. Baiocchi G, Rocha RM; Vulvar cancer surgery. Curr Opin Obstet Gynecol. 2014 Feb;26(1):9-17. doi: 10.1097/GCO.0000000000000033.
15. Iavazzo C, Johnson K, Savage H, et al; Sexuality issues in gynaecological oncology patients: post treatment symptoms and therapeutic options. Arch Gynecol Obstet. 2014 Sep 27.
16. Lawrie TA, Patel A, Martin-Hirsch PP, et al; Sentinel node assessment for diagnosis of groin lymph node involvement in vulval cancer. Cochrane Database Syst Rev. 2014 Jun 27;6:CD010409. doi: 10.1002/14651858.CD010409.pub2.
17. Meads C, Sutton AJ, Rosenthal AN, et al; Sentinel lymph node biopsy in vulval cancer: systematic review and meta-analysis. Br J Cancer. 2014 Jun 10;110(12):2837-46. doi: 10.1038/bjc.2014.205. Epub 2014 May 27.

18. Wills A, Obermair A; A review of complications associated with the surgical treatment of vulvar cancer. Gynecol Oncol. 2013 Nov;131(2):467-79. doi: 10.1016/j.ygyno.2013.07.082. Epub 2013 Jul 14.
19. Lai J, Elleray R, Nordin A, et al; Vulval cancer incidence, mortality and survival in England: age-related trends. BJOG. 2014 May;121(6):728-38; discussion 739. doi: 10.1111/1471-0528.12459. Epub 2013 Oct 22.
20. Deka P, Barmon D, Shribastava S, et al; Prognosis of vulval cancer with lymph node status and size of primary lesion: A survival study. J Midlife Health. 2014 Jan;5(1):10-3. doi: 10.4103/0976-7800.127784.

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