

Invasive vulval cancer

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Abstract

Vulval cancer is rare accounting for 0.7% of all new cases of female cancers and represents about 4 % of all gynaecological malignancies. Squamous cell carcinoma is the most frequent histological subtype of cancer of the vulva followed by malignant melanoma. Although predominantly considered as a disease of postmenopausal women, there has been a significant increase in rates of vulval cancer in younger women possibly due to increasing incidence of premalignant lesions of vulva caused by human papilloma virus infection.

Management of vulval cancer has evolved into an individualized multidisciplinary approach, and patients should be referred centrally to a gynaecological cancer centre where all relevant expertise is available. Usual treatment of vulval cancer includes surgical excision of primary lesion and lymph node assessment by sentinel node dissection or inguinofemoral lymphadenectomy. Radiotherapy can be added to the above treatment if there is high risk of disease recurrence or to control residual disease when repeat surgery is not feasible. The mainstay of treatment is surgery and the disease itself as well as treatment carries long-term physical and psychological sequelae. Although survival rates are high for those with negative groin nodes, the morbidity associated with standard radical techniques has prompted innovation for less radical approach such as sentinel node detection.

This review highlights the current understanding of the aetiology, pathophysiology and management of vulval cancer.

Keywords human papilloma virus; inguinofemoral lymphadenectomy; sentinel node detection; squamous cell carcinoma; vulval intraepithelial neoplasia; wide local excision

Introduction

Vulval cancer represents about 4–5% of the gynaecological malignancies with a global burden of disease estimated as 27,000 women each year. The European age-standardised incidence rate is 2.5 per 100,000 female population and the estimated life-time risk of developing vulval cancer is around 1 in 293 for women in the UK. In England, the Office for National Statistics (ONS) reports that, for 2010, there were 967 new cases and over 300 deaths from vulval cancer. Mortality rates for vulval cancer in the UK have declined steadily since the early 1970s. The rate fell by almost half (48%) from 1.3 per 100,000 female population in 1971 to 0.7 per 100,000 in 2008.

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Prognosis is strongly correlated to lymph node involvement and therewith the stage of disease. The five-year survival rate for node-negative patients following surgery is 70–90% but falls to 25–40% if nodes are involved.

Although the overall incidence rate for vulval cancer in the UK has been fairly stable, a significant increase is noticed in younger women over the last three decades. This has been linked to increasing incidence of vulval intraepithelial neoplasia (VIN) in young women caused by human papilloma virus (HPV) infection. Changes in sexual practice leading to greater exposure to HPV and smoking are likely causes for these increased rates. Several studies have associated increased rates of vulval cancer with lower socio-economic status and fewer years of education.

No screening guidance exists for early detection of vulval cancer and therefore symptom awareness is very important especially for the women with increased risk. Additionally, women with carcinoma of the vulva are at an increased risk of developing other genital cancers, particularly cervical cancer. Similarly, women with invasive intraepithelial disease of the cervix are at an increased risk of developing invasive and pre-invasive vulval and vaginal lesions.

In recent years, there has been an increase in the efforts to change surgical practice with emphasis on more conservative surgical techniques. The above move is largely due to a higher number of young and sexually active women being affected with this disease and increase in awareness of associated physical and psychosexual morbidity. Vulval cancers are now managed in a tertiary cancer centre within the context of a multidisciplinary team of experts led by a specialist gynaecological oncologist.

Predisposing factors

Possible aetiological factors for vulval carcinoma are vulval intraepithelial neoplasia (VIN), HPV infection, squamous hyperplasia, lichen sclerosus, smoking and immunosuppression. There appears to be two distinct patterns of developing vulval cancer based on the primary underlying vulval condition and the patient's immune status. The two aetiological pathways include one related to HPV and seen in younger women, while the other is HPV-independent and tends to affect older women. Amongst this bimodal pattern of vulval cancers, the HPV-dependent cancer often appears in more than one location and is associated with VIN.

Vulval intraepithelial neoplasia (VIN)

VIN has become an increasingly recognized clinical problem. Although initially thought to be a disease of low malignant potential in all cases, it is now recognized that VIN develop along two separate pathogenic pathways: HPV-associated and HPV-independent. The incidence of VIN has increased substantially in developed countries over the last three decades. It is unclear whether this rise would be followed by a rise in incidence of vulval cancer. However, it does contribute to cancer in persistent disease states. Human papilloma virus (HPV) infection is found in association with high-grade VIN in approximately 90% of cases. Histologically, VIN displays varying degrees of cytoplasmic and nuclear maturation, abnormal nuclei, disruption of normal architecture, and mitotic figures. VIN can present with pruritus vulvae, pain and ulceration although 20–45% will be asymptomatic.

The older classification system of VIN 1 (mild dysplasia), VIN 2 (moderate dysplasia), and VIN 3 (severe dysplasia) was revised in 2004 (Table 1). The former classification system did not reflect biological observation that VIN 1 is not considered a precursor for invasive cancer and just reflects reactive or HPV-related changes. Also, the diagnosis of VIN 1 is not reproducible among observers. Therefore, the term VIN 1 is no longer used.

In the current classification system, there are two types of VIN. The first is known as VIN, usual type (warty, basaloid, and mixed). This category includes both VIN 2 and 3, tends to occur in younger women, and is HPV-related. The second is known as VIN, differentiated type. This is seen in the setting of lichen sclerosus or squamous cell hyperplasia (lichen simplex chronicus), and is more common in older women. This is generally not associated with HPV infection. With this high-grade VIN, there is good agreement among observers on the diagnosis. Differentiated VIN is regarded as a high-grade lesion that always warrants further evaluation and treatment. Women with VIN 3 require careful follow-up and surgical excision remains the gold standard treatment for unifocal VIN.

Human papilloma virus

The proportion of vulval carcinomas associated with HPV infection varies from 15% to 79%. HPV16 is by far the most common type identified in both vulval carcinomas and VINs, although other HPV types, such as 18, 31, 33, and 45, have also been reported. Low-risk HPV types, especially HPV6 and HPV11, have been found in a small percentage of vulval lesions, but their role is not clear. HPV is detected in most cases of undifferentiated VIN (usual type) and only in few cases of differentiated VIN.

Prophylactic HPV vaccines, which cover HPV16 and HPV18, have been associated with a significant reduction in the incidence of VIN in young women. Thus, a decrease in the incidence of vulval lesions associated with HPV infection is expected to occur

in the future because of the development of these prophylactic vaccines, which have become a promising new tool for the prevention of HPV-associated premalignant and malignant lesions.

The viral oncoproteins E6 and E7 have a main role in cellular transformation. E6 degrades the tumour suppressor p53, abrogating its function, and consequently leading to the absence of cell cycle arrest. The HPV oncoprotein E7 inactivates the retinoblastoma tumour suppressor gene product, resulting in hyperproliferation of host cells and overexpression of the cell cycle related biomarkers p16^{INK4a} and p14^{arf}. Therefore, HPV-associated premalignant lesions and carcinomas show diffuse immunostaining for p16^{INK4a} and p14^{arf}, and are negative for p53. It has also been shown that vaccination with synthetic long peptides from the HPV16 oncoproteins E6 and E7 seems to have a therapeutic effect on HPV16-positive VIN.

Lichen sclerosis (LS)

Lichen sclerosis is a chronic inflammatory disease with fibrosis of the vulva and anogenital skin. The exact aetiology remains unknown, but autoimmune involvement has been suggested as a possible mechanism, and there is certainly association with other autoimmune diseases such as thyroid disorders, alopecia areata, pernicious anaemia, type 1 diabetes and vitiligo. Presentation is usually with intense vulval itching, but soreness or burning may be the primary symptom, particularly where there has been chronic itch. Pruritus is often worse at night and many women have disturbed sleep. Lichen Sclerosis often begins as a sharply demarcated, raised, non-specific erythema of vulva. Fragility of skin is a hallmark of LS which results into erosions, fissuring, purpura, and ecchymoses. The typical lesions are porcelain-white papules and plaques with hyperkeratosis. Subsequently, the lesion evolves into a dry, hypopigmented, sclerotic, and later atrophic lesion. The resulting crinkling or cellophane paper-type appearance is pathognomonic. Lichen sclerosis has a 3–5 % risk of progression to vulval cancer. These figures may underestimate the risk due to undiagnosed and unreported cases of LS. The use of topical steroids and general skin care advice can help break the itch–scratch cycle and reduce the risk. Long-term follow up at regular intervals of 6–12 months, patient education for change in appearance of lesions and ongoing supportive treatment in primary or secondary care settings are essential for optimal management of this debilitating condition.

Lichen planus (LP)

Lichen planus is a rare mucocutaneous disorder commonly affecting mouth and probably of autoimmune origin. Genital LP presents with intense vulval itching, pain, soreness, dyspareunia and bleeding. If vagina is involved, a purulent discharge can be present due to desquamative vaginitis. Erosive lichen planus makes vulva appear “red raw” with often no specific erosions. LP can often be misdiagnosed as LS because of similarity in presentation. Appearance of the lesions, vaginal involvement and histology helps to diagnose lichen planus. Progression to malignancy is reported as rare and treatment is with topical steroids and hydrocortisone suppositories in the case of erosive lichen planus.

Old and new classification systems for vulval intraepithelial neoplasia

Old	New
VIN 1 (mild atypia; loss of differentiation of the lower 1/3 of the epidermis)	Flat condyloma or HPV effect
VIN 2 (moderate atypia; loss of differentiation in the lower 2/3 of the epidermis)	VIN, usual type (uVIN)
VIN 3 (severe atypia; loss of differentiation of the entire epidermis but with an intact basement membrane)	VIN, warty type
Differentiated VIN, simplex type	VIN, basaloid type
	VIN, mixed (warty/basaloid) type
	VIN, differentiated type (dVIN)

Table 1

Paget's disease

Extramammary Paget's disease of the vulva is a rare vulval intraepithelial neoplasia of unknown aetiology and seen in postmenopausal women. The main symptom is localized itch. The lesion is large, red, moist, and sharply demarcated with crusting and eczematous appearance. Paget's disease can be associated with an underlying vulval adenocarcinoma (4–8%) and adenocarcinoma elsewhere (<15%). Therefore, investigation for other tumours of gastrointestinal, urinary tracts and the breasts is advised. Surgical excision is recommended to exclude adenocarcinoma of vulval skin. Despite obvious clinical features, surgical margins are difficult to achieve owing to subclinical disease, and recurrence is common.

Cigarette smoking

There is evidence from case–control studies of an increased risk of vulval squamous cell carcinoma (SCC) for smokers. Cigarette smoking is an established cofactor to HPV in the development of vulval squamous cell carcinoma, and may influence risk through an immunosuppressive pathway. The risk is significantly worse for smokers who are seropositive for high risk HPV16. Genetic variation in interleukin 2 (IL2) with the inhibition of HPV-targeted immunity may modify the effect of smoking on the risk of HPV-related vulval cancers. The proportion of women with VIN who are current smokers has been reported as 32–84%. There is little or no increased risk for those who are former cigarette smokers. No groups distinguished the frequency of smoking between the two types of VIN, but it is generally believed that cigarette smoking is strongly associated with VIN, usual type. This type, like other forms of lower genital tract carcinoma in situ, is more frequent among immunocompromised women.

Squamous cell carcinoma is the most frequent form of cancer of the vulva, and many cases, particularly in younger women, are HPV-related. Malignant melanoma, Bartholin's gland tumour, adenocarcinoma, basal cell carcinoma and a variety of sarcomas account for the remaining vulval tumours (Table 2).

Histological types

Histological type	Approximate % of total vulval cancers
Squamous cell carcinoma	90%
Melanoma	5%
Bartholin's gland tumour	2–3%
Adenocarcinoma arising from Bartholin's gland or in association with Paget's disease	<1%
Verrucous carcinoma	<1%
Sarcomas:	1–2%
Includes fibrosarcomas, neurofibrosarcomas, liposarcomas, rhabdomyosarcomas, angiosarcomas, epitheloid sarcomas and malignant schwannomas	

Table 2

Squamous cell carcinoma

These tumours (Figure 1) are divided into two groups: keratinizing SCCs unrelated to HPV (>70% of cases), and warty and basaloid carcinomas associated with high-risk HPV (<25% of cases). Keratinizing SCC presents as exophytic or ulcerative tumours. Microscopically, the tumour is composed of invasive nests of malignant squamous epithelium with central keratin pearls. The lesions grow slowly, extending to contiguous skin, vagina, and rectum. They metastasize initially to superficial inguinal lymph nodes, and then to deep inguinal, femoral, and pelvic lymph nodes.

Malignant melanoma

Although uncommon, malignant melanoma is the second most frequent cancer of the vulva (5%). It occurs in the sixth and seventh decades but occasionally is found in younger women. Most vulval malignant melanoma arise in the clitoris (31%) and labia majora (27%). The clinical presentation is that of a pigmented, flat, or polypoid asymmetrical lesion. Other presentations include bleeding, itching and presence of satellite lesions. Vulval melanoma is usually managed by wide local excision alone as the assessment of groin nodes mainly provides prognostic rather than therapeutic benefit. The main prognostic factors are tumour thickness on histology and clinical status of groin nodes. Melanomas invading <1 mm on histology and negative node status can have improved survival rates up to 90%. The overall survival rates are estimated at 47%.

Bartholin's gland tumour

It is usually an adenocarcinoma arising from the mucin-secreting columnar epithelial cells of the acini or squamous carcinoma



Fig. 1 Squamous cell vulval carcinoma affecting the clitoris and upper vulva in a close approximation with external urethral meatus.

arising from the squamous epithelium at the vestibular orifice of the duct. The utmost leading symptom is a painless visible mass in the posterior part of the labium majus. Most of the lesions look like a cyst or an abscess that fail to resolve following treatment. Adenoid cystic carcinoma (ACC) is a rare histological variant accounting for approximately 15% of all Bartholin's gland malignancies. This histological type is a slow growing and has similar behaviour as ACCs occurring in salivary glands, the upper respiratory tract and skin. Treatment is same as management of SCC of the vulva.

Basal cell carcinoma

Basal cell carcinomas of the vulva are identical to their counterparts in the skin. They are not associated with HPV, rarely metastasize, and are usually cured by surgical excision with a small margin.

Verrucous carcinoma

This histological variant of invasive SCC is unusual and typically occurs in postmenopausal women. These are locally invasive somewhat indolent condylomatous fungating tumours. The tumours are characterized by exophytic "cauliflower-like" lesions. Their microscopic appearance is hallmarked by acanthosis with a well-differentiated squamous epithelium with minimal cellular atypia. The margins of these tumours are often referred to as 'pushing'. They rarely show lymphovascular space invasion and metastasis from these tumours is uncommon. Treatment is by radical surgical excision however the formal lymphadenectomy is typically omitted.

Vulval sarcomas

Sarcomas arising in the vulva are rare and are often misdiagnosed clinically as Bartholin gland cysts. Leiomyosarcomas are most common and often present as an enlarging, painful mass, usually on labia majora. Treatment is wide local excision, and adjuvant radiotherapy may be beneficial. Lymphatic metastasis is uncommon and overall survival rates are approximately 70%.

Clinical presentation of vulval cancer

The vast majority of the women with vulval carcinoma are symptomatic. The common symptoms that prompt a rapid referral to the gynaecological department include presence of a mass and an ulcerated lesion on vulva. The other symptoms include pain, burning, bleeding, pruritus, and discharge. Any woman presenting with such symptoms should undergo clinical examination.

Despite the high incidence of symptomatic lesions, delay in diagnosis (typically 4–6 months) and referral is common. Many women will delay presentation due to embarrassment and primary care physicians may delay an examination for similar reasons or inadequate facilities to carry out examination in the community. The other reason for delay is a trial of topical therapy for nonspecific symptoms with no appropriate follow-up. Therefore if such therapies are tried out, arrangements should be made for a short-term review of the patient to assess improvement and those with no change in condition should be

referral for further assessment and biopsy if appropriate. It is worth mentioning that genital "warts" in postmenopausal women are often SCCs and should be biopsied. Other concerning features are ulcers, hyperpigmentation, depigmentation, irregular skin contour, a fungating mass or groin lymphadenopathy. Most SCCs are unifocal and confined to labia majora.

Malignant melanoma presents as enlarging pigmented lesion most commonly on labia minora or clitoris and often does not have other symptoms. Women who present with persistent Bartholin's abscess or cyst should raise a suspicion of Bartholin's gland carcinoma. The vulval lesions associated with BCC can appear as a rodent ulcer with rolled edges and usually less than 2 cm situated on anterior labia majora.

Diagnosis and investigations

Vulval lesions with clinical suspicion of cancer should be biopsied to provide histological confirmation of diagnosis and permit further planning of appropriate intervention. Most biopsies should be carried out as punch or wedge biopsies using local anaesthesia. Adequate depth to include dermis and connective tissue is essential for histological evaluation of the depth and nature of stromal invasion. Biopsy should be taken from the edge of the lesion to include adjacent normal epithelium. Centre of the lesion usually undergoes necrosis and therefore biopsy should be avoided from this region. Dissolvable suture may be required to achieve haemostasis.

While assessing a patient with suspicious vulval lesion, if appropriate, assessment of cervix and vagina should be carried out for other squamous intraepithelial lesions or malignancy. Therefore vulval lesions are best assessed in colposcopy clinic settings. If the measured lesion is very small it is possible to obtain a wide local excisional biopsy. A clearance margin of at least 1 cm, including depth, is required. In such cases, clinical photograph of the lesion should be taken to provide precise record of the site of the lesion before it is excised. Excisional biopsies should also be considered if there is marked discrepancy between clinical and histological examination as false negative biopsies of invasive lesions have been reported in literature. Women with extensive local disease may require examination under anaesthesia to establish the extent of adjacent spread to urethra, bladder, anus or rectum. Such examinations are usually performed by gynaecological oncologists in conjunction with radiation oncologists and plastic surgeons. Routine imaging with computed tomography (CT) or magnetic resonance imaging (MRI) for pelvis or abdomen is not required unless tumour extension to urethra, anus, vagina or pubic bone is suspected (Figure 2).

Assessing nodal spread

Accurate identification of nodal metastases has a direct influence on the choice of initial surgery. Clinical assessment of loco-regional lymph nodes is inaccurate, with a sensitivity of 57 % and a specificity of 62 % and only detects the superficial groin nodes. Imaging techniques such as ultrasound, computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) have been assessed and used with varying success. Ultrasound based techniques are highly

operator dependent. Clinically suspicious nodes can be sampled in the outpatient setting using fine needle aspiration (FNA) or ultrasound-guided core biopsy, however these techniques carry high false-negative rates due to sampling error. Magnetic resonance imaging (MRI) can identify abnormal nodes based on their size and shape with a higher degree of specificity but with lower sensitivity.

Staging

Vulval SCC is staged surgically and the International Federation of Gynecology and Obstetrics (FIGO) classification system (Table 3) is used. Mortality is directly related to the stage of disease at presentation. The survival rate depends on stage of cancer and the overall five-year survival rate is approximately 58%. For stage 1 and 2, the five-year survival rates are 79% and 59% respectively while the survival rates drop to 43% and 13% for stage 3 and 4 vulval cancers. Vulval melanomas are staged differently using the Clark or Breslow modifications of the micro staging system. Depth of invasion is measured from the deepest point of the tumour to the epithelial-stromal junction of the adjacent most superficial dermal papilla.

The pattern of disease spread is by direct extension to adjacent tissues followed by lymphatic embolization and is influenced by tumour type. Initial lymphatic spread is to local inguinal nodes followed by femoral and external iliac chain. Haematogenous spread is uncommon. Lymph node involvement can occur early in the disease process thereby supporting the embolic spread theory.

Frailty assessment

Most women with vulval SCC belong to elderly age group and therefore co-existing medical conditions are frequent. The recommendations of the consensus meeting held during the 6th

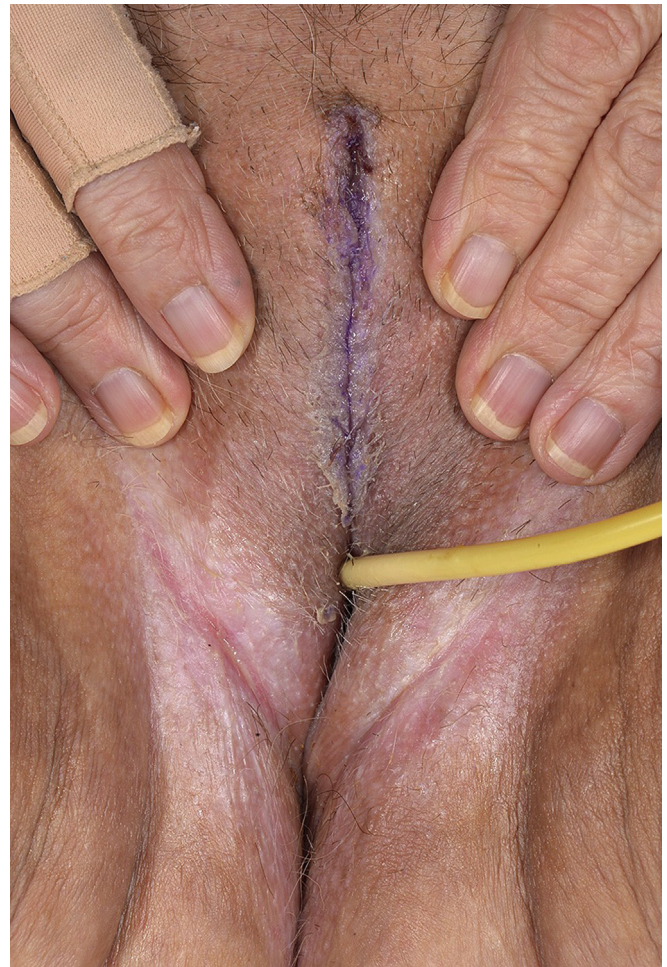


Fig. 3 Post-surgery appearance after a radical wide local excision with primary closure of vulval cancer.

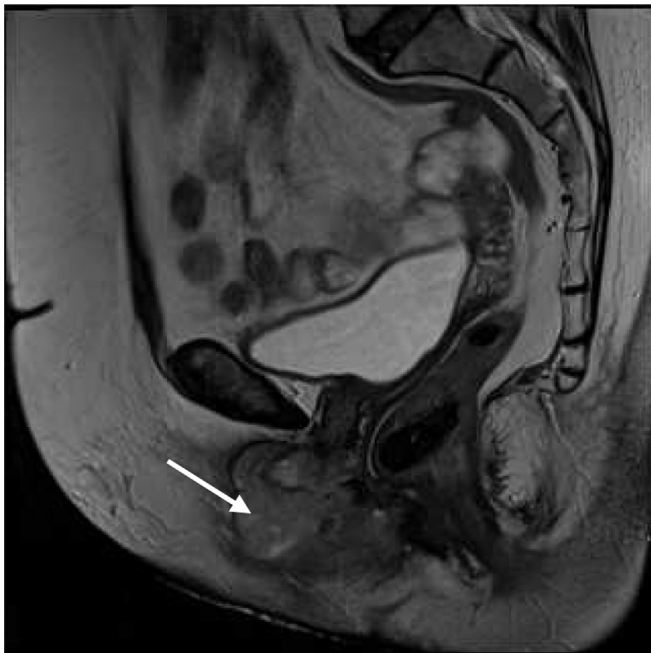


Fig. 2 An MRI (T2 weighted) to identify tumour spread to adjacent structures such as urethra and pubic symphysis.

International Conference on Geriatric Oncology was that any elderly cancer patient should firstly be assessed on his/her frailty, and then considered for appropriate cancer management. The assessment of performance status may provide useful pre-operative prognostic information and has been shown to be an independent predictor of survival in women over the age of 80. Currently available risk assessment tools include ACE-27 (Adult Co-morbidity Evaluation-27), ASA (American Society of Anesthesiologists) scoring system, APACHE (The Acute Physiological and Chronic Health Evaluation), POSSUM (Physiological and Operative Severity Score for EnUmeration of Mortality and Morbidity) as well as Portsmouth modification of POSSUM (P-POSSUM). Early involvement of physiotherapy, occupational therapy and social services are essential components of care package for a frail patient.

Management

The broad principles of managing vulval cancers include management of primary tumour and that of inguinofemoral nodes/nodal disease. The two categories for the primary tumour include early and advanced disease.

In the UK, most vulval cancers are managed by a multidisciplinary team in a cancer centre. Surgery remains the treatment of

Staging of cancer of the vulva (adapted from FIGO CANCER REPORT), 2012

FIGO stage	Description
I	Tumour confined to the vulva
IA	Lesions ≤ 2 cm in size, confined to the vulva or perineum and with stromal invasion ≤ 1.0 mm ^a , no nodal metastasis
IB	Lesions > 2 cm in size or with stromal invasion > 1.0 mm ^a , confined to the vulva or perineum, with negative nodes
II	Tumour of any size with extension to adjacent perineal structures (lower third of urethra, lower third of vagina, anus) with negative nodes
III	Tumour of any size, with or without extension to adjacent perineal structures, with positive inguinofemoral nodes
IIIA (i)	With 1 lymph node metastasis (≥ 5 mm), or
(ii)	With 1–2 lymph node metastasis (es) (< 5 mm)
IIIB (i)	With 2 or more lymph node metastases (≥ 5 mm)
(ii)	With 3 or more lymph node metastases (< 5 mm)
IIIC	With positive nodes with extra-capsular spread
IV	Tumour invading other regional (upper 2/3 urethra, upper 2/3 vagina), or distant structures
IVA	Tumour invades any of the following: (i) upper urethral and/or vaginal mucosa, bladder mucosa, rectal mucosa, or fixed to pelvic bone, or (ii) fixed or ulcerated inguinofemoral lymph nodes
IVB	Any distant metastasis including pelvic lymph nodes

^a The depth of invasion is defined as the measurement of the tumour from the epithelial–stromal junction of the adjacent most superficial dermal papilla to the deepest point of invasion.

Table 3

choice although radiotherapy and chemotherapy plays a role. Previously, women underwent radical surgery in the form of radical vulvectomy with *en bloc* bilateral inguinofemoral lymphadenectomy through a single butterfly incision. Although effective, this approach is associated with significant complication rates. This radical surgery with “butterfly resection” is replaced by triple incision technique to avoid the co-morbidities associated with butterfly incisions. The aim of surgery is

Lymph node involvement according to depth of invasion

Depth of invasion, mm	No. patients	Positive nodes	% Positive
< 1	163	0	0
1.1–2	145	11	7.6
2.1–3	131	11	8.4
3.1–5	101	27	26.7
> 5	38	13	34.2
Total	578	62	10.7

Adapted from NHS Executive. Improving Outcomes in Gynaecological Cancer.

Table 4

Surgical excision margin and Risk of local recurrence

Series	Margin < 8 mm, n/N (%)	Margin > 8 mm, n/N
Heaps	21/44 (48%)	0/91
Chan	12/53 (23%)	0/30
De Hullu	9/40 (23%)	0/39

Table 5

adequate local disease control by obtaining adequate disease-free surgical margins and appropriate management of groin lymph nodes with either sentinel node dissection or inguinofemoral lymphadenectomy. Treatment plans should be individualized and should take into account patient's age, fitness, sexual function, tumour size, tumour site, stage of disease and patient's wishes.

Surgical treatment for early vulval cancer

Patients with very early vulval carcinomas measuring less than 2 cm in maximum diameter, confined to the vulva and perineum and with a depth of invasion (DOI) less than 1 mm (FIGO stage 1A) are at very low risk of lymph node metastasis ($< 1\%$) and can be managed with wide local excision only (Table 4). Wide local excision is utilized in place of a traditional disfiguring hemi- or total vulvectomy. Tumours with DOI > 1 mm (FIGO stage 1B or worse) or maximum diameter > 2 cm (FIGO stage II or worse) requires groin node dissection with removal of primary tumour with adequate margins. Nowadays, the primary tumour is removed as wide local excision or radical wide local excision to reduce psychosexual morbidity from *en bloc* resection. Depending on the size of the wound defect after removing the lesion with adequate margins, the patient may either require a primary closure of the wound or surgical flap-based skin graft.

The important parameter of wide local excision surgery is adequate histological margin. A histological margin of less than 8 mm is associated with high recurrence rate (up to 50 %), whereas a margin of 8 mm or greater is associated with a very low recurrence rate (Table 5). To achieve a histological margin of 8 mm it is usually necessary to take a measured margin of 15 mm in all the planes (medial, lateral and deep) and the deep margin should be the inferior fascia of the urogenital diaphragm, which is co-planar with the fascia lata and the fascia over the pubic symphysis. This is because the specimen contracts following excision and fixation. If the lesion is close to urethra, the distal 1 cm of the urethra is resected without significant effect on urinary continence. Certain radical wide local excisions may require the gynaecologists to mobilize simple cutaneous or fasciocutaneous flaps for smaller excisions. If appropriate, superficial excision of associated VIN should also be also carried out.

For larger lesions myocutaneous flaps are used and usually requires support from plastic surgeons. Lateral vulval tumours only require ipsilateral groin node dissection initially. If the ipsilateral groin nodes are found to be positive for metastasis contralateral lymphadenectomy may also be required. Lateral tumours are defined by their location of more than 1 cm from the midline structures such as clitoris, urethra, vagina, perineal body and/or anus.

Surgical treatment in advanced disease

The aims of treatment in advanced disease are similar to early stage disease: treat the primary tumour and management of groin and pelvic nodes. As most patients are elderly, management needs to be tailored to individual patient's needs, their wishes, associated medical co-morbidities and performance status. Pre-operative imaging of chest, abdomen and pelvis is essential to assess the extent of disease.

Excision of larger lesions may involve important structures such as urethra or anus with resultant co-morbidity such as urinary or faecal incontinence. More extensive excisions can also result in difficulties of wound healing, wound breakdown, scarring, impaired sexual function and psychosexual sequelae. Exenterative procedures require multidisciplinary pre-operative examination involving plastic surgeons, urologist and colorectal surgeons to tailor treatment having regard to patient's wishes and likely prognosis.

Pelvic lymph node metastases have been reported in approximately 5–15 % of all vulval tumours. However, their involvement is unlikely without the involvement of inguinofemoral lymph nodes. The rate of pelvic lymph node recurrence increases with the number and size of groin node metastases. Radiotherapy is favoured to treat deep nodes rather than pelvic lymphadenectomy in appropriate cases.

Management of groin lymph nodes

The value of appropriate groin node dissection should not be underestimated, as it allows adequate staging and therefore, remains an important factor in reducing the mortality from vulval cancer. The incidence of lymph node metastasis is related to clinical stage of the disease and depth of invasion. A recurrence in the groin carries a very high mortality. Systematic inguinofemoral lymphadenectomy comprises resection of superficial inguinal lymph nodes as well as deep femoral nodes and selective superficial inguinal lymphadenectomy constitutes under-treatment with significant risk of recurrence and associated rise in mortality rates. Patient selection is important due to the significant morbidity associated with lymphadenectomy. Lymphadenectomy is not required in early stage 1A vulval cancer due to the very low risk of metastasis. Therefore majority of the patients with early stage disease may undergo an unnecessary lymph node resection and the associated complications. Complications include wound dehiscence, infection, lymphocysts and lymphoedema (Table 6).

In a median tumour location (lower commissure, peri-urethra, peri-clitoris) and stage 1B cancer, bilateral inguinofemoral lymphadenectomy should be carried out. For the lateral tumours, an ipsilateral lymphadenectomy is sufficient since the risk of contralateral lymph nodes involvement is less than 1 %. In the case of ipsilateral positive lymph nodes, the other side has to be removed. Adjuvant radiotherapy should be considered when a single groin node is completely replaced by tumour or two or more lymph nodes are involved with microscopic metastatic disease or extra-capsular spread in any node. There is no evidence that radiation to both sides compared to the involved side only provides greater benefit. However, if one groin side is positive and the other side has not been dissected, both groins and the pelvis should be considered

Complications arising during surgical management of vulval cancer

Timing of complications	Complication
Early (up to 6 weeks after surgery)	Femoral nerve injury leading to anaesthesia of anterior thigh Deep vein thrombosis/pulmonary embolism Wound infection and breakdown – vulva or groin or both Wound necrosis or graft rejection Osteitis pubis Haemorrhage including femoral blow out Groin lymphocysts or seroma of femoral triangle Urinary tract infection Urethral mucosal prolapse (UMP)
Late (6 weeks after surgery or later)	Chronic leg oedema and Recurrent leg lymphangitis Dyspareunia/psychosexual complications Introital stenosis Femoral hernia Cystocele, rectocele Faecal incontinence or Urinary stress incontinence

Modified from Hacker, 2000.

Table 6

for treatment. In node positive cases, adjuvant treatment should be given to the groins and the pelvic nodes due to better two-year survival rates with this approach compared to the pelvic lymphadenectomy.

Suspicious/enlarged groin nodes

Clinically suspicious nodes can be biopsied using outpatient or ultrasound guided FNA and a pre-operative CT scan should be carried out to check for distant metastases. Groin radiotherapy can reduce the recurrence rate significantly. An operation without radiotherapy is considered insufficient. Because of the high morbidity of an inguinofemoral lymphadenectomy, which is even worse when completed by radiotherapy, a complete lymphadenectomy in this locally advanced disease is not desirable. A debulking of large lymph nodes ought to be carried out, followed by radio-chemotherapy.

Role of sentinel node dissection

Sentinel lymphadenectomy is a standard procedure in surgery of breast cancer and malignant melanoma. Sentinel node detection has been investigated as a safe, accurate method of ascertaining the status of clinically non-suspicious groin nodes pre-operatively to allow inguinofemoral lymphadenectomy, with all its attendant morbidity, to be restricted to patients who need it.

Sentinel node detection involves injection of intradermal isosulfan blue dye around primary vulval lesion, either alone or

commonly with a ^{99m}Tc radioactive sulphur colloid. Sentinel node is the node that receives primary lymphatic flow from tumour and is detected positive by uptake of radioactive colloids and blue dye. Central tumours may have bilateral sentinel nodes. The negative predictive value for dual technique of sentinel node detection is quoted between 89 and 100 %. The finding of a positive node with metastasis would lead to full systematic lymphadenectomy, but those with negative node would be spared the significant morbidity associated with procedure. Sentinel node detection should only be performed by appropriately trained gynaecological oncologist within a skilled multidisciplinary team.

Sentinel lymphadenectomy is associated with a lower rate of lymphoedema compared to complete groin lymphadenectomy. Nevertheless, the procedure has a small but definite false negative rate ($\sim 2\%$) therefore appropriate counselling of risks and benefits and close surveillance is paramount as the groin recurrence in vulval cancer carries a very poor prognosis.

Positive groin nodes

Radiotherapy is most frequently used in the management of involved groin nodes. If there is micro-metastasis affecting just one lymph node then adjuvant radiotherapy is not usually recommended, as groin recurrence is unlikely. However, if there is replacement of one or more nodes with tumour, and particularly if there is extra-capsular spread then adjuvant radiotherapy is usually given to reduce the risk of recurrence. Radiotherapy is typically given as EBRT to the inguinal and lower pelvic nodes although some clinicians have questioned the additional benefit of treating the pelvic nodes. Neo-adjuvant radiotherapy (EBRT brachytherapy) may be useful in the treatment of women with fixed inguinal nodes and for those in whom surgical treatment would involve exenteration, where the use of neo-adjuvant radiotherapy may facilitate more conservative local surgery.

Radiotherapy

Like other squamous cell carcinomas, vulval SCCs are very sensitive to radiation. Radiotherapy can be used in management of vulval cancer as primary or adjuvant treatment. Radiotherapy has shown to improve the treatment outcomes however it can lead to significant morbidity and could be particularly distressing in patients with post-surgery physical and psychological morbidities. External beam radiotherapy (EBRT) is used to treat inguinofemoral or groin nodes while brachytherapy can be used to treat primary lesions either in isolation or a booster dose following EBRT.

Primary radiotherapy

Primary radiotherapy may be used in cases of unresectable vulval disease or medical co-morbidities. Vulval skin tolerates radiation very poorly and therefore the primary treatment in early stage disease should be surgical. Pre-operative radiotherapy or chemo-radiation can reduce the tumour size in bulky unresectable disease and may allow more conservative local

surgery or sphincter-sparing surgery in case of anal involvement.

Adjuvant radiotherapy

Two factors influence the need for radiotherapy in an adjuvant setting: surgical margins of resected specimen and involvement of groin nodes with metastasis. Other factors which may influence the decision to give adjuvant radiotherapy include the presence of an infiltrative growth pattern and lymphovascular space involvement both of which are associated with increased risk of local recurrence but not of the nodal metastasis. In patients with positive nodes after a radical surgery, adjuvant radiotherapy significantly improves survival. A randomised GOG study showed 28% improvement in survival due to decreased incidence of groin recurrence after adjuvant radiotherapy. Radiotherapy is not usually recommended if there is micro-metastasis affecting a single groin node. With regards to the surgical margins, the risk of local recurrence increases as the disease-free margins decrease. Adjuvant radiotherapy for patients with close or involved margins does improve local control and has a survival benefit compared to surveillance alone. The other option would be to consider surgical re-excision. However, close surveillance with surgical salvage at recurrence is also a valid approach in selected cases.

Recurrent disease

Recurrence of vulval cancer is seen in about one third of the patients and the risk is influenced by FIGO stage greater than II, positive nodal status and vascular space invasion. The increasing trend towards more conservative primary surgery may be associated with higher rates of local recurrence. Therefore, careful follow-up is essential to detect recurrence at an early stage and allows for curable treatment to be offered. Most recurrences occur within two years of initial treatment and poorer prognosis is associated with nodal or distant recurrence. Repeat excision is the preferred treatment for recurrence localized on the vulva. Use of reconstructive techniques to preserve function needs to be considered for such repeat procedures. However, wound healing could be a major issue especially if the excisional field has received radiotherapy during initial surgery. Groin node recurrence or skin-bridge recurrence may be managed with radiation and surgery whereas chemotherapy regimens (cisplatin, cyclophosphamide and/or bleomycin) may be employed for distant disease.

Palliative treatment

Vulval SCC with advanced stage and fungating, bulky disease requires individualized treatment plans in discussion with the woman, her family or her carers. These tumours can cause significant symptoms such as progressive lymphoedema, wound care, uncontrolled bleeding, urinary or bowel complications and acute or chronic pain. They may not be amenable to curative surgery or radiotherapy. Palliative vulvectomy may be necessary to remove the tumour and very large, symptomatic groin nodes can be removed at the same time. Palliative care services should be involved from the outset in management of such patient.

Quality of life and psychosexual issues

The objective evidence from research with regards to quality of life and psychosexual issues after vulval cancer surgery is limited. Vulvectomy patients can experience disruption of sexual activity, decline in body image, and significant levels of distress compared with healthy patients. The changes in sexual function may include dyspareunia secondary to introital narrowing from scarring and loss of genital architecture. In one study women who underwent radical wide local excision or vulvectomy demonstrated disruption to sexual excitement and orgasm but sexual desire was not diminished. Sexual outcome correlated with degree of surgical intervention with more conservative excision better preserving sexual function.

Issues with wound breakdown and delayed wound healing may have psychological impact and should be adequately addressed to minimize the risk of longer-term psychological effects, such as depression, social isolation and loss of role in society. Caring for a patient with a fungating lesion when cancer progresses or recurs can offer many challenges. Therefore, it is important to ensure that patients' individual needs and wishes are addressed, to promote optimum quality of life.

Summary

Vulval cancer is rare and so should be managed in specialist cancer centres with a multidisciplinary approach. If diagnosed and treated early, vulval cancer carries an excellent prognosis however, both early and late disease has associated physical and psychological sequelae. The trend towards increasing incidence of VIN and VIN-related cancer in the younger female population is of public health concern and these patients should be kept under surveillance jointly by primary and secondary care and should be managed with active interventions as required in order to allow for timely diagnosis and better outcome.

Recent years have seen a huge change in how patients are involved in the process of decision making. The role of cancer nurse specialist is vital throughout diagnosis, treatment and post-operative care. There are exciting developments in vulval cancer that are leading to improved outcomes, preservation of function and reduction in morbidity. The development and implementation of vulval sentinel node procedure is a major breakthrough in how we care for patients with vulval cancer. Dual morbidity of complete lymphadenectomy followed by radiotherapy if nodes are positive can now be avoided with use of sentinel node dissection of positive nodes. Sexual dysfunction is a distressing consequence of vulvar surgery that needs to be recognized by health professionals and addressed with patients pre-operatively. Loss of sexual desire, feeling of loss of femininity, lowered self esteem and depression are also associated with radical vulval cancer surgery. Thus, the clinical and non-clinical needs to care for a patient with advanced vulval cancer can be multifaceted. These challenging requirements mean that optimal oncologic treatment of vulvar cancer patients can only be made available by centralization of resources. Furthermore, it will also be necessary for design and recruitment of the urgently needed prospective controlled trials in this still relatively rare disease. The role of chemotherapy in conjunction with surgery and/or

radiotherapy is also under investigation to determine the impact of the various treatment modalities with respect to morbidity and patient quality-of-life. ◆

FURTHER READING

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Practice points

- Vulval cancer is a very rare disease and, on average, a general practitioner will only see a new case once every 7 years.
- There should be a high index of suspicion for abnormal lesions on vulva, including 'warts' in the postmenopausal woman. Any woman with persistent vulval symptoms needs clinical examination.
- Diagnostic biopsy in a suspected vulval cancer should be an incision rather than excision biopsy. If excision biopsy has to be carried out, it must include a zone of normal tissue of at least 1 cm in width and depth.
- Histological diagnosis of cancer must be obtained before definitive surgery and surgical intervention should be carried out by specialist gynaecological oncologist.
- Inguinofemoral lymphadenectomy should be carried out in squamous cell carcinoma of vulva with depth of invasion > 1 mm. Inguinofemoral lymphadenectomy is not required when depth of invasion < 1 mm or melanoma with clinically uninvolved nodes, verrucous carcinoma or basal cell carcinoma.
- Bilateral inguinofemoral lymphadenectomy is required in medial tumours or large lateral lesions of > 2 cm. Ipsilateral inguinofemoral lymphadenectomy should be performed for lateral tumours < 2 cm diameter. If the nodes are positive, contralateral inguinofemoral lymphadenectomy should be performed.
- Primary tumour should be excised with a minimum of 15 mm of clear margin which allows for a minimum of 8 mm clear margin on histopathology.
- Radiotherapy is indicated with ≥ 2 involved nodes or bilateral nodal involvement or extra-capsular spread.
- For early disease, sentinel node biopsy may have a role in reducing the morbidity of surgery.