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. 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.

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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.

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, warty type VIN, basaloid type VIN, mixed (warty/basaloid) type
VIN 3 (severe atypia; loss of differentiation of the entire epidermis but with an intact basement membrane)	
Differentiated VIN, simplex type	VIN, differentiated type (dVIN)

Table 1

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.