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Review of the current surgical management of vulval cancer

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Abstract

Currently in the United Kingdom, 1200 cases of vulval cancer are diagnosed per annum accounting for 6% of female genital cancers. Although classically a condition that affects older women and associated with lichen sclerosus, there has been a greater incidence of vulval squamous tumours in young women due to the increasing prevalence of promoting human papillomavirus (HPV). The advent of a vaccination programme against HPV 16 and 18, the main aetiological causes of vulval intraepithelial neoplasia and cervical intraepithelial neoplasia, may reduce the incidence in future generations. Primary surgery is the current gold standard treatment and although mortality rates have reduced by 40% since the 1970s, radical vulval resections are associated with significant morbidity such as wound breakdown, infection, lymphoedema and psychosexual consequences. Over the past decade there has been a move to less mutilating procedures in women diagnosed with early vulval cancer. This is in combination with the introduction of new surgical methods such as sentinel lymph node testing, more directed radiotherapy and chemotherapy options. These treatment methods are being assessed in clinical trials to determine their associated recurrence rates, survival rates and morbidity. Most vulval cancers are squamous cell in origin but, there are other histological subtypes including Paget's disease and vulval melanoma which can require different management approaches. The objective of this paper is to review the current literature on the management of vulval cancer, summarise the new treatments which are being developed and the associated evidence.

Key words: Vulval cancer; Paget's disease; Human papilloma virus; Sentinel lymph nodes; Inguinofemoral groin node dissection

Core tip: One thousand and two hundred cases of vulval cancer are diagnosed annually in the United Kingdom. Primary surgery is the current gold standard treatment but radical vulval resections are associated with significant morbidity so there has been a move to less mutilating surgical procedures. Sentinel lymph node testing, more directed radiotherapy and chemotherapy

are all currently being assessed in clinical trials and the advent of the HPV vaccination programme may reduce the incidence in future generations. The objective of this paper is to review the current literature on the management of vulval cancer and summarise the new treatments and the associated evidence.

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INTRODUCTION

Currently in the United Kingdom, 1200 cases of vulval cancer are diagnosed per annum accounting for 6% of female genital cancers[1]. Due to the increasing prevalence of promoting human papillomavirus (HPV), the incidence of vulval squamous tumours has been increasing in young women[2]. The advent of a vaccination programme against HPV 16 and 18, the main aetiological causes of vulval intraepithelial neoplasia (VIN) and cervical intraepithelial neoplasia (CIN), may reduce the incidence in future generations[3]. Primary surgery is the current gold standard treatment and although mortality rates have reduced by 40% since the 1970s, radical vulval resections are associated with significant morbidity such as wound breakdown, infection, lymphoedema and psychosexual consequences[1,4-6]. Over the past decade there has been a move to less mutilating procedures in women diagnosed with early vulval cancer and this review paper outlines the current trends in treatment of women with vulval cancer, both early and advanced.

RESEARCH

A systematic literature search was performed using PubMed, Cochrane and EMBASE, using search criteria of "vulval cancer - early and late", "Paget's disease of the vulva", "sentinel lymph node testing in vulval cancer", "HPV and vulval cance" and "surgery, radiotherapy and chemotherapy for vulval cancer". Fifty-four papers were identified and thirty were directly referenced in this review paper.

DISCUSSION

Treatment of early cancer

For the management of stage Ⅰ and Ⅱ (Table 1), current studies have advocated a policy of "less is more"; wide local excision (WLE) reduces the significant morbidity associated with radical vulvectomy and recurrence rates are low[7,8]. It is recommended that tumours should be excised, ideally with a 2-cm excision margin down to the inferior fascia of the urogenital diaphragm and the fascia over the symphysis pubis[9]. Studies suggest that microscopic excision margins beyond 8 mm are associated with low recurrence rates, whilst margins less than 8 mm carry a recurrence rate of around 50%[10]. Moreover, larger surgical excision margins allow for the reduction and contraction of tissues following pathological preparation techniques. The dissection of inguino-femoral lymph nodes is dependent upon the depth of invasion and the site of the tumour; lateral tumours have more than 1 cm of healthy tissue beyond the WLE which does not affect midline anatomy and drain to the ipsilateral groin node. Resection of these nodes alone is safe with similar recurrence rates to bilateral dissection if the contralateral vulva is disease free[7,11]. With midline lesions, which occur less frequently, bilateral groin node dissection is required but pelvic lymph node dissection is not necessary due to the recognised pattern of lymphatic drainage[11].

Table 1 Staging system for vulvar cancer of the international federation of gynaecology and obstetrics

IA	Tumour confined to the vulva or perineum, ≤ 2 cm in size with stromal invasion ≤ 1 mm, negative nodes
IB	Tumour confined to the vulva or perineum, > 2 cm in size or with stromal invasion > 1 mm, negative nodes
II	Tumour of any size with adjacent spread (1/3 lower urethra, 1/3 lower vagina, anus), negative nodes
IIIA	Tumour of any size with positive inguino-femoral lymph nodes (1) 1 lymph node metastasis greater than or equal to 5 mm (2) 1-2 lymph node metastasis(es) of less than 5 mm
IIIB	(1) 2 or more lymph nodes metastases greater than or equal to 5 mm (2) 3 or more lymph nodes metastases less than 5 mm
IIIC	Positive node(s) with extracapsular spread
IVA	(1) Tumour invades other regional structures (2/3 upper urethra, 2/3 upper vagina), bladder mucosa, rectal mucosa, or fixed to pelvic bone (2) Fixed or ulcerated inguino-femoral lymph nodes
IVB	Any distant metastasis including pelvic lymph nodes

Hacker *et al*[12] 1993 investigated the correlation between depth of invasion and nodal involvement (Table 2). The evidence suggests that women with early vulval cancer (FIGO Ia) are at very low risk of nodal involvement if the depth is less than 1 mm and WLE alone is appropriate in this cohort. Women with a FIGO stage IB and above have a significant risk of groin node metastasis and therefore bilateral resection is recommended.

A Cochrane Review has assessed randomised control trials which have compared primary radiotherapy of the inguinofemoral lymph nodes to inguinofemoral lymph node dissection in women with early stage vulval cancer. This review concluded that groin node recurrence rates were increased (RR = 10.21, 95%CI: 0.59-175) with primary radiotherapy but lymphoedema was reduced (RR = 0.06, 95%CI: 0.00-1.03) and so were life-threatening cardiovascular complications (RR = 0.08, 95%CI: 0.00-1.45). Even though the review only included one study, which had a small number of participants (n = 52), it appears safer to excise the lymph nodes at present until the outcome of larger

Table 2 Correlation between depth of invasion and nodal metastasis in vulval SCC

Depth of invasion	Percentage of positive nodes
< 1 mm	0%
1-2 mm	7.6%
2-3 mm	8.4%
3-5 mm	26.7%
> 5 mm	34.2%

randomised control trials are available[13].

Lymph nodes

The method of lymph node dissection has also moved towards more conservative approaches: *En bloc* "butterfly" dissection has been replaced by the triple incision technique[14]. Additionally, there is some evidence that preservation of the fascia lata and saphenous vein can reduce the post-operative morbidity of lymphoedema without jeopardising outcome[15].

Recent advances in the management of vulval cancer have focused on sentinel lymph node testing. As lymph node metastases are only present in 30% of women with early vulval cancer, a significant number of women will be at risk of substantial postoperative morbidity and have negative lymph nodes. Different techniques to identify sentinel nodes have been used in trials, based on experience with different cancer types such as breast cancer and cutaneous melanoma. The best detection rates are seen when a combination of blue dye and technetium-based tests are used[16]. The GROINSS-Ⅵ trial concluded that patients with early stage vulval cancer and a negative sentinel node have low rates of groin recurrence (2%-3%), excellent survival rates at 3 years (97%) and minimal morbidity[17]. Groin recurrence with positive nodes was reported as 9%. However, other studies have suggested that detection rates and recurrence rates can vary significantly and the trial concluded that an element of quality control is required to ensure that an adequate level of surgical expertise and experience is present within an institution. Sentinel node techniques are therefore best suited to larger centres with higher case numbers. Additionally, data on longer-term recurrence is limited[18]. The GROINSS-Ⅶ trial is ongoing and seeks to treat patients with metastatic sentinel lymph nodes directly with radiotherapy instead of inguinofemoral lymphadenectomy followed by radiotherapy, thus theoretically reducing the morbidity of dual modality treatment[17]. In this trial, radiotherapy alone is restricted to patients with sentinel node metastases measuring ≤ 2 mm due to the known poor prognosis associated with sentinel node metastases measuring over 2 mm[19].

Adjuvant therapies

Adjuvant radiotherapy is offered to all patients who are found to have positive lymph nodes. The recent AGO-CaRE-1 study indicated that prognosis is improved in node positive patients, although when compared to those patients who are node negative the overall prognosis is poorer. Progression-free survival at 3 years was 39.6% in lymph node positive patients receiving adjuvant radiotherapy, 25.9% in LN positive patients without adjuvant treatment and 75.2% in lymph node negative patients[20]. It has been suggested that prognosis may be improved with the use of chemoradiation rather than radiotherapy alone, as this has been successful in the management of other squamous cell cancers such as anal and cervical cancer. No randomised controlled trials have yet been performed, but initial studies have indicated good clinical responses with acceptable toxicity[2].

Treatment of advanced vulval cancer

FIGO stage 3 and 4 tumours are characterised by local extension, pain, discharge, bleeding and odour. Management can be very difficult, particularly as lymph node metastases are present in approximately 50% and can ulcerate into the groin or can be fixed to the femoral vessels[14]. These patients have the option of ultra-radical surgery involving partial or total pelvic exenteration with the burden of a urostomy or colostomy, or treatment with chemotherapy or radiotherapy[21,22]. Results and prognosis can be poor, with symptom control often being the preferred option.

Post-operative complications and psychosexual consequences

The drive for a move towards more conservative surgery is related to the significant morbidity associated with excision of vulval lesions and lymph node dissection. Patients often have post-operative wound infections or dehiscence, prolonging hospital stays and require ongoing outpatient care. Moreover, inguinofemoral lymph node removal is associated with wound breakdown, lymphocyst formation, infection, lower limb lymphoedema and chronic cellulitis[23].

Excision of the clitoris, distortion of the vulval anatomy and changes to bowel and bladder function can also have significant psychological effects[24]. Many patients will become sexually inactive, and as expected, this trend seems to increase with the extent of surgical excision[25].

Paget's disease of the vulva

Extramammary Paget's disease can rarely affect the vulva (1%-5% of vulval malignancies), and is defined as an intraepidermal adenocarcinoma. The management is primarily surgical, but can be particularly complex to manage due to a multicentric pattern and irregular margins, resulting in up to 44% local recurrence rates[26]. Paget's disease can be sub-classified into intraepithelial and invasive types, with a significantly greater recurrence rate in invasive lesions of 67% compared with 9% in intraepithelial lesions over a median follow-up period of 69 mo in a recent study by

Nomura *et al*[27]. Distant metastases tend to be rare, with management focusing on surveillance and repeat surgical excisions. Alternative treatments that have been used with varying effects are local and systemic chemotherapy, radiotherapy, photodynamic therapy, laser therapy and Moh's micrographic surgery.

Impact of a HPV vaccine

The development and implementation of a vaccine against the highly oncogenic HPV genotypes 16 and 18, which account for 70% of CIN and VIN, have been projected to decrease the incidence and morbidity of pre-cancerous and cancerous genital disease. Indeed, the Future II trial, a randomised control trial which compared women given a HPV vaccine to placebo, showed a vaccine efficacy of 75% for low grade warty or basaloid VIN[28].

Despite these promising results, HPV is the main aetiological cause in only 30%-40% of invasive vulval cancers[29]. Differentiated VIN is responsible for 65%-80% of vulval cancers and arises in older women (55-85 years old) with concomitant vulval dermatoses such as lichen sclerosis, lichen planus or lichen simplex. Other histological subtypes include melanomas (3%), Bartholin's gland tumours (5%), adenocarcinomas (< 1%) secondary to Paget's disease and sarcomas (1%-2%)[3]. It seems apparent that the predicted decrease in incidence of cervical cancer following the introduction of the vaccine may not have such significant effects on the prevalence of vulval cancer, particularly in the aging population. Management of this cohort needs to be individualised to their medical comorbidities and therefore topical treatments such as Imiquimod and Cidofovir are being investigated to determine their efficacy in treating VIN so the morbidity of surgery, as outlined in this review, can be circumvented. Studies have shown a reduction of 25% in lesion size over 20 wk of treatment but this has to weighed against the acute discomfort following application of the cream and the lack of long term data assessing recurrence rates[30].

CONCLUSION

This overview of vulval cancer management summarises the current surgical approach, with an emphasis on conservative surgery that minimises the risk of recurrence whilst maintaining body function. There are important developments being made in the introduction of new management methods, most notably sentinel node testing. Current practice is limited by the availability of evidence and therefore further trials investigating existing and novel surgical management of vulval cancer will be vital. The results of ongoing sentinel node trials will give more information on longer-term recurrence rates and streamlining treatment modalities. Furthermore, reviewing resection margins in a more formal trial setting would also be valuable, whilst other trials researching chemo-radiation and the role of HPV may further change the direction of vulval cancer management.

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