BRITISH GYNAECOLOGICAL CANCER SOCIETY

Royal College of Obstetricians & Gynaecologists

Guidelines for the Diagnosis and Management of Vulval Carcinoma

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Contents

Development of the document

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Summary of consensus statements

C There is no evidence to support screening an unselected population for vulval cancer.

C There is no evidence that the follow-up of women with uncomplicated lichen sclerosus needs to be hospital based.

C Women with high-grade vulval intraepithelial neoplasia (VIN), high-grade VIN with multicentric disease, VIN in the immunosuppressed and those with Paget's disease or melanoma in situ should be followed up in either specialist multidisciplinary vulval clinics or by gynaecological oncologists. This is to provide the full range of surgical treatments, reconstructive surgery, nonsurgical alternatives and colposcopic follow-up. Guidance for the assessment and management of women with vulval disorders is detailed in RCOG Green-top Guideline No. 58.[4]

C Women with Paget's disease of the vulva should have prolonged follow-up.

C Vulval cytology is not a substitute for diagnostic biopsy of suspicious lesions.

C In women where a vulval cancer is strongly suspected on examination, urgent referral to a cancer centre should not await biopsy.

C All cases of suspected vulval cancer should have the diagnosis confirmed with a biopsy and reviewed by the specialist multidisciplinary team prior to radical treatment.

C Diagnostic biopsies of suspected vulval cancer should be representative incisional biopsies, avoiding removal of the whole lesion.

C All vulval biopsies and excision specimens should be reported as advised by the Royal College of Pathologists' *Standards and datasets for reporting cancers. Datasets for the histopathological reporting of vulval neoplasms (3rd edition)*.[18]

B Wide radical local excision of the primary tumour with a minimum margin of 15 mm of disease-free tissue is often sufficient.

B Groin node surgery should be undertaken through separate incisions (triple incision technique) to reduce morbidity. The incidence of skin bridge recurrence in early-stage disease is low.

B In unifocal tumours of less than 4 cm maximum diameter where there is no clinical suspicion of lymph node involvement, patients can be safely managed by removal of the identified sentinel lymph nodes.

B In lateral tumours, only ipsilateral groin node surgery need initially be performed. Contralateral lymphadenectomy may be required if ipsilateral nodes are positive.

B Superficial groin node dissection alone should not be performed, as it is associated with a higher risk of groin node recurrence.

B Groin node dissection should be omitted in stage Ia squamous cancer, verrucous tumour, basal cell carcinoma and melanoma.

C Preservation of the long saphenous vein may reduce both groin wound and subsequent lower limb problems.

A Surgery is the cornerstone of therapy for the groin nodes in women with vulval cancer. Individual women who cannot be optimised to enable surgery can be treated with primary radiotherapy.

C Plastic surgery involvement may be required for large defects and when radiotherapy has been used. The vulva is a challenging area for wound healing and faecal and urinary diversion is often required.

B Groin node dissection should be omitted in stage Ia squamous cancer, verrucous tumour, basal cell carcinoma and melanoma.

B Sentinel lymph node biopsy should be offered to all eligible women with squamous carcinoma of the vulva.

C Vulval melanomas need to be jointly managed with the appropriate melanoma MDT.

A Surgery is the cornerstone of therapy for the groin nodes in women with vulval cancer. Individual women who are not fit enough to withstand surgery, even when performed under regional anaesthesia, can be treated with primary radiotherapy.

C Primary and recurrent vulval cancer does respond to chemotherapy but responses are variable and toxicity may be a problem in this population of patients.

C Future development of targeted therapy with drugs such as erlotinib through mutation testing may lead to improvement in vulval cancer treatment toxicity benefit ratio and provide effective systemic treatment even for the more infirm patients.

1. Background

Vulval cancer is rare. In the year 2010, there were 1172 new cases in the UK, giving a crude incidence rate of 3.7/100 000 women. It is ranked as the 20th most common female cancer.[1] The most recent mortality figures (2011) suggest a crude mortality rate of 1.3/100 000 women.[2] By age group, the incidence trend has remained relatively stable over the last three decades, although the incidence in women aged 40–49 years has risen two-fold. This increase has been reflected in reports from other countries and has been ascribed to the effect of increasing human papillomavirus (HPV) infection.[1]

This document covers all invasive vulval cancers of any histological type.

Vulval cancer is a disease affecting predominantly elderly women and is uncommon below the age of 50 years. Comorbidities also increase with age which may prove challenging when planning management.

As there will be occasions when clinical history and examination alone cannot exclude cancer or preinvasive disease, this document addresses issues of referral for investigation and confirmation, diagnostic procedures and management. The questions of follow-up and outcome assessment are also addressed.

1.1 Objectives

This document is intended to fulfil several objectives:

- To promote a uniformly high standard of care for women with vulval cancer
- To define standard approaches to treatment
- To encourage gynaecological oncologists to develop and participate in clinical trials involving new approaches to management
- To establish auditable standards.

1.2 Methodology

The authors have developed this consensus document, with input from British Gynaecological Cancer Society members. The authors have also drawn on the experience of previously published guideline materials and other relevant published texts. The document sets out achievable clinical standards and targets for all health professionals involved in the management of patients with vulval malignancy.

Classification of evidence

To ensure that the statements made in this document are evidence based, the current literature was reviewed and critically appraised. The reliability and quality of the evidence given throughout this document has been graded following the NHS Executive classification system, as follows:

Grade A: Based on randomised controlled trials (RCTs).

Grade B: Based on other robust experimental or good observational studies.

Grade C: More limited evidence but the advice relies on expert opinion and has endorsement of respected authorities.

1.3 Definitions of excision

Incisional biopsy

A biopsy taken with the intent of securing a diagnosis only. This should ideally contain the interface between normal and abnormal epithelium and be large enough for the pathologist to be able to adequately provide evidence of substage (in stage I cases).

Excisional biopsy

A biopsy taken that includes all of the abnormal epithelium but does not provide a tumour-free zone of 1 cm (after fixation) on all dimensions. This would normally be performed in cases of vulval intraepithelial neoplasia (VIN) or when there is a low suspicion of invasive carcinoma and the operator wishes to limit the amount of cosmetic harm.

Radical excision

An excision performed with the intent of achieving clearance of at least 1 cm (after fixation) on all aspect of the tumour(s). Depending on the site and size of the tumour, this could vary from a radical local excision to a radical vulvectomy.

2. Screening, diagnosis and presentation

2.1 Screening

Unselected population

There are no screening tests that have been shown to be of benefit in an unselected population. Self-examination is recommended by organisations such as the Vulval Pain Society, although there is no published evidence on whether this is beneficial or not. Given a common aetiological factor in many cases of vulval cancer is oncogenic HPV infection, some women with vulval cancer may benefit from a shorter cervical screening interval, but there is currently no evidence to support this.

C There is no evidence to support screening an unselected population for vulval cancer.

Women with conditions that predispose to vulval cancer

Lichen sclerosus and infection with high-risk types of HPV are both conditions in which squamous neoplastic change can be seen. There may be an intraepithelial stage seen first (vulval intraepithelial neoplasia, VIN) with either condition. This is known as differentiated VIN when it is associated with lichen sclerosus (d-VIN) and usual, classical or undifferentiated when it is HPV associated. It has been suggested that there is a higher risk of invasion in d-VIN,[3] but the diagnosis is often only made in association with a squamous cancer.[4,5] Typically HPV-related disease is seen in younger women and may be multifocal. Either disease may also be present in the perianal region.

The risk of developing invasive disease in women with lichen sclerosus is approximately 4%. It is not clear whether this risk is reduced by treatment. Women with uncomplicated lichen sclerosus do not require routine hospital-based follow-up, but should be informed of the risks of invasion. Those who have or have had VIN associated with lichen sclerosus should be followed up in the same manner as those with VIN.

C There is no evidence that the follow-up of women with uncomplicated lichen sclerosus needs to be hospital based.

In women with VIN (either lichen sclerosus related or HPV related), colposcopy is useful for localisation but the signs are nonspecific. Diagnosis is by biopsy. Multiple biopsies may be required to exclude invasion. Standard treatment is wide local excision. Medical treatment may be appropriate and consideration should be given to enrolment in an appropriate trial. The risk of recurrence following treatment is high and the risk of invasion approximately 4%. Follow-up should be either in specialist vulval clinics or by gynaecological oncologists.

C Women with high-grade vulval intraepithelial neoplasia (VIN), high-grade VIN with multicentric disease, VIN in the immunosuppressed and those with Paget's disease or melanoma in situ should be followed up in either specialist multidisciplinary vulval clinics or by gynaecological oncologists. This is to provide the full range of surgical treatments, reconstructive surgery, nonsurgical alternatives and colposcopic follow-up. Guidance for the assessment and management of women with vulval disorders is detailed in RCOG Green-top Guideline No. 58.[4]

Other pre-invasive conditions include Paget's disease (adenocarcinoma in situ) and melanoma in situ. These conditions are rare, but have a significant risk of invasion. As there is no large body of evidence on which to base practice, it may be best for them to be followed up in a clinic with a special interest in premalignant vulval disease. Prolonged follow-up for Paget's disease is suggested.[6,7]

C Women with Paget's disease of the vulva should have prolonged follow-up.

HPV testing is not a proven screening tool for vulval cancer and does not aid diagnosis, although it may be used as a research tool. Other aids to diagnosis have been described in women with pre-existing vulval disease, including toluidine blue and exfoliative cytology using scalpel scrapings or Dacron swabs. Results of studies are variable and none of these techniques is a replacement for biopsy of clinically suspicious lesions.[8–11]

C Vulval cytology is not a substitute for diagnostic biopsy of suspicious lesions.

2.2 Presentation

Vulval cancer is most common among women over 65 years old, but may present in women considerably younger. Presentation is often delayed.

Presentation will vary according to stage of disease. Women often have difficulty articulating vulval symptoms to medical practitioners and all women with vulval symptoms should be examined. Presentation usually comes in one of the following categories:

Incidental

Vulval cancers are sometimes diagnosed on examination during another procedure, for example colposcopy or catheterisation. Often these are not asymptomatic, but the women have either not presented for diagnosis, or not been appropriately referred.

During follow-up for pre-existing vulval disease

For example, lichen sclerosus or VIN; see section on screening.

Symptomatic

Symptoms of vulval cancer include vulval itching, irritation or pain. Women may also notice a lump, bleeding or discharge.

2.3 National Institute for Health and Care Excellence (NICE) guidance

The National Institute for Health and Care Excellence (NICE) guidance on referral for suspected vulval cancer (Clinical guideline 27; June 2005)[12] recommends the following:

- When a woman presents with vulval symptoms, a vulval examination should be offered. If an unexplained vulval lump is found, an urgent referral should be made (within the 2 week wait schedule).
- Vulval cancer can also present with vulval bleeding due to ulceration. A patient with these features should be referred urgently (within the 2 week wait schedule).
- Vulval cancer may also present with pruritus or pain. For a patient who presents with these symptoms and where cancer is not immediately suspected, it is reasonable to use a period of 'treat, watch and wait' as a method of management. But this should include active follow-up until symptoms resolve or a diagnosis is confirmed. If symptoms persist, the referral may be urgent or non-urgent, depending on the symptoms and the degree of concern about cancer.

2.4 Diagnosis

The cornerstone of diagnosis is examination and diagnostic biopsy.

While the need to take a full history is self-evident, specific questioning will also be required. Women often self-medicate with over-the-counter topical preparations that can exacerbate the symptoms of vulval cancer. Advice regarding care of the vulva and omitting these medications forms an important part of management.

Clinical features strongly indicating vulval cancer include an irregular, fungating mass, an irregular ulcer or enlarged groin nodes. Such patients should be referred urgently to a cancer centre without awaiting biopsy.

C In women where a vulval cancer is strongly suspected on examination, urgent referral to a cancer centre should not await biopsy.

Any change in the vulval epithelium in a postmenopausal woman warrants a biopsy.

These changes include: a swelling, polyp or lump, an ulcer, colour change (whitening or pigment deposition), elevation or irregularity of the surface contour. Any 'warts' in a postmenopausal woman or persistent 'warts' in the premenopausal woman should be biopsied. In premenopausal women all other vulval signs and symptoms should be managed as for those in postmenopausal woman unless there is a confirmed infection. Lesions should be biopsied rather than excised, as excision may preclude the use of sentinel node biopsy. If cancer is confirmed, the patient should be referred to a gynaecological cancer centre.

2.5 Biopsies

All diagnoses should be based upon a representative biopsy of the tumour that should include the area of epithelium where there is a transition of normal to abnormal tissue. Diagnostic biopsies should be of a sufficient size (greater than 1 mm depth to allow differentiation between superficially invasive and frankly invasive tumours) and orientated to allow quality pathological interpretation. Biopsies should be referred to a pathologist with a specialist interest in gynaecological pathology

(see section 3: Pathology).

There may be exceptions to these rules. If, for instance, an elderly woman with major medical problems and a severely symptomatic lesion presented, a small punch biopsy under local anaesthetic could provide adequate diagnostic information to allow planning of definitive therapy. In certain situations where the clinical diagnosis is apparent and the patient very symptomatic, i.e. heavy bleeding or pain, definitive surgery to the vulval lesion may be performed but biopsy with frozen section is recommended prior to proceeding with any radical procedure.

Although not essential, pre-biopsy photographs are of value in planning treatment, particularly if the diagnostic phase and treatment phases are conducted in separate centres.

When evaluating a vulval lesion, the size and location should be documented. The appearance of the background epithelium should be noted, particularly the presence of changes suggestive of lichen sclerosus, as this will affect postoperative treatment. Residual lichen sclerosus appears to have a significant risk of recurrence for vulval cancer.[13] Any involvement of the vagina, urethra, base of the bladder or anus should be noted. With large tumours, the tumour should be palpated to assess whether it is infiltrating deep to the pubic and ischial bones. The examination may have to be performed under general anaesthesia because of the pain often associated with large tumours. The presence or absence of groin lymphadenopathy should also be noted. Radical treatment of vulval cancer is associated with significant morbidity and therefore biopsy confirmation should be obtained beforehand.

C All cases of suspected vulval cancer should have the diagnosis confirmed with a biopsy and reviewed by the specialist multidisciplinary team prior to radical treatment.

C Diagnostic biopsies of suspected vulval cancer should be representative incisional biopsies, avoiding removal of the whole lesion.

3. Pathology

3.1 Microscopic

Ninety percent of all vulval cancers are squamous cell carcinomas, with melanoma, Paget's disease, Bartholin gland tumours, adenocarcinoma and basal cell carcinoma accounting for most of the remaining tumours. The histology is important, as it represents a variable in determining the likelihood of lymph node involvement.

The presence of infiltrative growth patterns, compared with a pushing pattern, is associated with a higher local recurrence rate. Presence of prominent fibromyxoid stroma at the invasive edge is associated with poorer outcome.[14] Lymphovascular space involvement (LVSI) is also associated with an increased local recurrence rate.[15] LVSI has not been associated with an increased risk of groin node metastasis. Both LVSI and infiltrative growth patterns are markers of poor prognosis but these factors do not indicate the need for adjuvant treatment.

Further research is required to establish the influence of these factors on the outcome of this disease.

3.2 Spread

Vulval cancer spreads by direct extension to adjacent structures, embolisation to the inguinal and femoral nodes (the regional lymph nodes) or by haematogenous spread. Overall, about 30% of women with operable disease have nodal spread.

3.3 Staging

Vulval cancer has been staged surgicopathologically using the International Federation of Gynecology and Obstetrics (FIGO) staging system since 1994 and has had various modifications, including a subdivision for stage I in 1994. The FIGO staging has been revised in 2009[16] and there have been four main changes:

- Stage II (> 2 cm) and Ib (< 2 cm) have been combined because these two categories of patients did not appear to differ in survival
- Patients with tumours involving the vagina and/or urethra with negative nodes are now classified as stage II (formerly stage III)
- Patients with positive nodes are still classified as stage III. The number and morphology (size and whether these have intra- or extranodal growth) of the involved nodes are taken into account.
- Bilaterality of positive nodes has been discounted.

The current FIGO staging is presented in Appendix 1.

3.4 Prognosis

The 5-year survival in cases with no lymph node involvement is in excess of 80%. This falls to less than 50% if the inguinal nodes are involved and 10–15% if the iliac or other pelvic nodes are involved. A multifactorial analysis of risk factors in squamous vulval cancer demonstrated that nodal status and primary lesion diameter, when considered together, were the only variables associated with prognosis.[17]

3.5 Histology

All vulval biopsies and excision specimens should be reported as advised by the Royal College of Pathologists' *Standards and datasets for reporting cancers. Datasets for the histopathological reporting of vulval neoplasms (3rd edition)*.[18]

3.6 Clinical information

The clinician should provide an accurate description of the site and appearance of the gross lesion. The request should also indicate whether the biopsy was excisional or diagnostic. Ideally, large radical resections should be pinned out on corkboard, kept moist with normal saline and sent as fresh tissue to the pathology department as rapidly as possible. If this is not possible, the specimen should be carefully orientated by means of marker sutures prior to fixation in the usual way.

3.6.1 Reporting the specimens

Squamous cell carcinoma:

This is the most common malignancy of the vulva. The report should describe:

- Vulval intraepithelial neoplasia
  - Classical type grade I, II and III
  - VIN differentiated type.

Assessment of invasion:

- Tumour type according to World Health Organization (WHO) classification
- Tumour differentiation
- Depth or thickness of invasion
- Presence or absence of vascular invasion
- Presence or absence of non-neoplastic epithelial disease.

In case of excision specimens:

- Assessment of margins
- Distance to epithelial resection margin
- Distance to urethral resection margin (if appropriate)
- Distance to vaginal resection margin (if appropriate)
- Distance to anal resection margin (if appropriate)
- Distance to soft tissue (deep) resection margin.

In cases with lymph node dissection, each lymph node must be examined histologically. Resected lymph nodes not involved macroscopically must be examined in their entirety with nodes larger than 5 mm blocked out at 2–3 mm. Nodes smaller than 5 mm are embedded whole. Levels are recommended in all sentinel node samples and in groin lymphadenectomy, if there are suspicious

groups of cells. The report must record total numbers of sampled lymph nodes, presence or absence of lymph node metastases, presence of extranodal spread and whether > 50% of any one node is involved. In the case of examining sentinel lymph nodes, the GROINSS-V II protocol should be followed until such a time as the procedure is endorsed by NICE.

The report must record the following core data items:
- Tumour type according to the WHO classification
- Tumour differentiation
- Tumour size (in at least two dimensions)
- Thickness/depth of invasion
- Presence or absence of lymphovascular invasion
- Status of all resection margins
- Minimum tumour-free margins
- Presence of associated VIN or Paget's disease
- Status of resection margins for VIN or Paget's disease
- Minimum distance to margins for VIN or Paget's disease
- Presence or absence of non-neoplastic epithelial disease
- Presence or absence of lymph nodes metastases
- Presence of extranodal spread
- Whether > 50% of any one node is involved.

3.7 Ancillary studies

3.7.1 Frozen sections

There is little use of frozen sections in surgical treatment of vulval malignancy.

3.7.2 Immunohistochemistry

It has a limited role in diagnosis of squamous cell carcinomas. Immunohistochemistry for broad-spectrum cytokeratins such as AE1/AE3 can be used to reveal micrometastases in sentinel nodes. Presently it is used routinely in research but awaits further evidence before use in routine practice.

Immunohistochemistry is valuable in differential diagnosis of Paget's disease. The neoplastic cells in primary vulval Paget's disease are positive for CAM 5.2, CEA, EMA and CK7. Diffuse CK20 positivity is suggestive of secondary vulval Paget's disease. This results from spread of an internal malignancy, most commonly from an anorectal adenocarcinoma or urothelial carcinoma of the bladder or urethra, to the vulval epithelium. Paget's disease may mimic melanoma on routine stains and immunohistochemistry for melan A, S100 and HMB45 may be used to confirm a melanoma.

Immunohistochemistry can be useful in differential diagnosis of vulval soft tissue lesions.

C All vulval biopsies and excision specimens should be reported as advised by the Royal College of Pathologists' *Standards and datasets for reporting cancers. Datasets for the histopathological reporting of vulval neoplasms (3rd edition)*.[18]

4. Treatment of primary disease

The treatment of vulval cancer is primarily by surgery. This has become more individualised and conservative although the need for adequate resection margins (1 cm after tissue fixation) and groin node dissection or evaluation remain important basic principles. The impetus for more conservative approaches stems from the well recognised psychosexual sequelae and from the morbidity associated with groin node dissection.[19,20] Reconstructive surgery has a role in the management of these cancers. Radiotherapy is used in the adjuvant setting and with or without chemotherapy and surgery in advanced disease.

Management may vary considerably from quite simple to very complex. Each case should be considered on its merits and an agreed plan of management devised by the gynaecological cancer team. Factors such as tumour size, location, medical fitness and the wishes of the patient will all influence management. The management of the nodes and the primary tumour should be considered on their own merits. Tumours should be staged using the most recent FIGO or TNM (tumour, nodes and metastases) classifications. FIGO staging is surgical–pathological and not clinical (Appendix 1).

It should be emphasised that these patients are often elderly and have significant comorbidities. As such, they require access to skilled anaesthesia services including an epidural service, high dependency and/or critical care. A key component of patient management is skilled nursing care. All of these services should be available in a cancer centre.

The major developments since the publication of RCOG guidance in 2006 have been the development of targeting groin lymph node biopsies (sentinel lymph node biopsies, SLNB) and a gradual increase in the number of women having some form of reconstructive or plastic surgery input. The latter is covered in an additional section on plastics and reconstruction. The indications for and use of SLNB is now included in this section.

4.1 Surgery

4.1.1 Early-stage disease

Depth of invasion

Lesions less than 2 cm in diameter and confined to the vulva or perineum, with stromal invasion less than or equal to 1.0 mm (FIGO stage Ia) can be managed by wide local excision only, without groin node dissection. This is because the risk of lymph node metastases is negligible.[21]

Dissection of the groin nodes (unilateral or bilateral) should be performed when the depth of invasion is greater than 1 mm (FIGO stage Ib or worse) or the maximum diameter of the tumour is greater than 2 cm.[22] This surgery can often be undertaken through separate groin and vulval incisions (triple incision technique) to reduce morbidity. The incidence of skin bridge recurrence in early-stage disease is very low.[23]

Published evidence suggests that unifocal tumours of less than 4 cm maximum dimension might safely be managed by excision of the sentinel lymph nodes identified in either groin.[24] Appropriate use of the sentinel node technique is covered in the following section on groin node dissection.

Surgery to the primary tumour should be radical enough to remove the tumour with adequate margins. The incidence of vulval recurrence has been shown to be related to the measured disease-free surgical margin, as measured in the fixed histopathological specimen. Given the reduction and contraction of tissues following excision and fixation, this equates to at least a 15 mm margin on the fresh surgical specimen. The risk of recurrence increases as the disease-free margins decrease (> 8.0 mm: 0%; < 8.0 mm, 47%).[15,23] Therefore, wide radical local excision with a minimum margin of 15 mm of disease-free tissue on all margins should be sufficient.

Excision of atypical skin (lichen sclerosus or VIN) affecting the remainder of the vulva should be considered, as these areas might contain separate foci of invasion and pose an increased risk of recurrence.[13] Removal of any lichen sclerosus or VIN (usual type and differentiated VIN) need not be to the same depth as that for invasive disease unless occult invasion is suspected.

A preoperative vulvoscopy and mapping biopsies may help in the planning of surgery.

When the surgical margins are found to be less than 1 cm, it may be appropriate to perform a further local resection, although evidence is lacking that this will result in a reduction in local recurrence. There is insufficient evidence to recommend adjuvant local therapy routinely in patients with close surgical margins.

B Wide radical local excision of the primary tumour with a minimum margin of 15 mm of disease-free tissue is often sufficient.

B Groin node surgery should be undertaken through separate incisions (triple incision technique) to reduce morbidity. The incidence of skin bridge recurrence in early-stage disease is low.

B In unifocal tumours of less than 4 cm maximum diameter where there is no clinical suspicion of lymph node involvement, patients can be safely managed by removal of the identified sentinel lymph nodes.

Lateral vulval tumours

Extensive cross-over of lymphatic channels of the vulva may result in nodal involvement of the contralateral groins in addition to the ipsilateral groin nodes. Therefore, bilateral groin node dissection is usually required. A lateralised lesion is defined as one in which wide excision, at least 1 cm beyond the visible tumour edge, would not impinge upon a midline structure (clitoris, urethra, vagina, perineal body, anus). Lymphatic cross-over is less likely in lateral tumours; therefore, only an ipsilateral groin node dissection need initially be performed.[25] If the ipsilateral nodes are subsequently shown to be positive for cancer, the contralateral nodes should also be excised or irradiated, as the nodes are more likely to be positive in this scenario.

A similar concept applies to the use of sentinel lymph nodes. If a sentinel lymph node can only be identified in the ipsilateral groin then the contralateral dissection can be omitted. If the SLNB is negative then no further surgery is necessary. If the SLNB is positive then consideration should be given to completion lymphadenectomy of both groins.

B In lateral tumours, only ipsilateral groin node surgery need initially be performed. Contralateral lymphadenectomy may be required if ipsilateral nodes are positive.

4.1.2 Groin node dissection

The greatest single factor in reducing mortality from vulval cancer is appropriate groin node dissection. However, groin node dissection should be omitted if the patient has stage Ia disease, as the incidence of lymph node metastases is negligible.[21] When a complete lymphadenectomy is indicated, it is recommended that the superficial inguinal nodes, as well as the deep femoral nodes, be removed. Superficial inguinal node dissection alone is associated with a higher risk of groin node recurrence.[22] Preservation of the long saphenous vein is reported to reduce both groin wound and subsequent lower limb problems,[26] although there are data that have not confirmed this and all studies have been observational and uncontrolled. Following inguinofemoral lymphadenectomy, sartorius muscle transposition may be of benefit in preventing subsequent femoral vessel damage, particularly in those women who are thin and in those in whom adjuvant groin radiation therapy is anticipated.[27] There is some suggestion that the number of groin nodes resected per groin is of relevance to groin relapse and this may have implications for surveillance.[28] However, the number of glands in the groin is very variable with fewer being harvested in elderly patients. Furthermore, there are no robust data on the accuracy of surveillance post surgery either clinically or with cross-sectional imaging.

B Superficial groin node dissection alone should not be performed, as it is associated with a higher risk of groin node recurrence.

B Groin node dissection should be omitted in stage Ia squamous cancer, verrucous tumour, basal cell carcinoma and melanoma.

C Preservation of the long saphenous vein may reduce both groin wound and subsequent lower limb problems.

4.1.3 Sentinel lymph node biopsy (SLNB)

Dye studies and lymphoscintigraphy may be of value in the detection of sentinel nodes.[29–31] There is a growing body of evidence demonstrating the safety and practicality of this intervention with significant improvements in postoperative morbidity without any significant compromise in accuracy or outcomes in terms of relapse.

As with all new techniques, their introduction should be undertaken with due regard to patient safety and should be audited closely. Ideally, all patients having SLNB should be enrolled in ongoing clinical studies such as GROINSS-V II. All surgeons undertaking these procedures should do so after appropriate training and demonstration of competency. The environments should be fully compliant with radiation protection protocols. Maintenance of skills and the requirement for robust audit would also suggest that such procedures should be limited to centres that have an adequate volume of work.

Eligibility for sentinel lymph node biopsy

The following eligibility criteria are the result of a series of studies culminating in the GROINSS-V I study that identified scenarios where the accuracy of SLNB was either uncertain or unproven. This has resulted in the following eligibility criteria:

- Primary squamous vulval cancers
- Cancers measuring less than 4 cm in maximum dimension
- Macroscopic unifocal cancers
- No clinical or radiological evidence to suspect lymph node metastasis
- No known safety issues for the use of Patent Blue dye and/or technetium-99

- Informed patient consent and acceptance of close follow-up (recommended 2-monthly in the first year).

If a sentinel lymph node cannot be identified following peritumoural injection of technetium-99 and/or Patent Blue dye then the patient should be considered for a complete inguinofemoral lymphadenectomy and should be counselled to this end at the time of consenting.

4.1.4 Advanced vulval cancer

Surgery to the primary lesion

Resection of advanced disease involves careful preoperative planning and, if reconstruction is required, this should be planned jointly with a plastic surgeon. Ideally a joint examination under anaesthesia (EUA) should be performed with the plastic surgeon. The size and location of the tumour will influence the surgical approach. Wide, radical, local excision with a minimum of 15 mm disease-free margin may be used but some tumours will require a radical vulvectomy. If these surgical approaches risk sphincter damage leading to urinary or faecal incontinence, treatment by radiotherapy should be considered, either with curative intent or to reduce tumour volume to permit less destructive surgery. Two studies have suggested that preoperative radiation in advanced vulval cancer reduced the need to perform defunctioning stomas.[32,33] It should be noted that, in this post-radiation setting, surgery can be more complicated and there is increased morbidity. All management options with their risks and benefits should be discussed with each patient.

Reconstructive surgical techniques should be employed to enable primary surgical closure and to reduce morbidity due to scarring. It should be stressed that the published experience of post-radiation surgery is limited and should not be undertaken lightly. Anovulvectomy might still be considered as an option in selected cases. This is an area where further research is vital. Consideration should be given in some cases to performing a diverting stoma 1–2 weeks before the definitive vulval surgery.

Management of clinically suspicious groin nodes

Groin node dissection should be undertaken when there are clinically suspicious groin nodes present. In cases with large primary lesions and clinically suspicious nodes, a radical vulvectomy with 'en bloc' groin node dissection should be considered.[21] In cases with fixed or ulcerated groin nodes, surgery and/or radiotherapy should be considered. There are no data suggesting the superiority of one treatment over the other, although, if surgery is used, it is likely that postoperative radiation will also be required. Pathological assessment of these nodes should be undertaken prior to radiotherapy, preferably by fine-needle aspiration cytology, in order to maximise the chances of maintaining skin integrity and minimising the risk of wound problems.

Multimodality treatment is increasingly used in the management of advanced vulval cancer to allow for sphincter preserving surgery and as an alternative to surgery for histologically proven involved groin lymph nodes. Surgery following groin radiation may, however, be associated with increased morbidity, both in the groin and in the lower limb. Overall, surgery should still be considered the cornerstone of therapy for the groin nodes.

A Surgery is the cornerstone of therapy for the groin nodes in women with vulval cancer. Individual women who cannot be optimised to enable surgery can be treated with primary radiotherapy.

4.2 Reconstructive surgery

Reconstructive surgery should be considered for patients where a major resection is planned and there is doubt as to whether direct closure of the wound will be possible. Care should also be taken in patients with recurrent disease who have previously been treated with radiotherapy as the tissues will be less compliant and more prone to wound breakdown. Involvement of a plastic surgeon in these cases is advised.

Vulval reconstruction presents a challenge for several reasons.

- The vulva and surrounding structures present a complex three-dimensional shape which can be difficult to recreate. Flaps can be bulky and skin grafts are prone to graft loss due to shearing forces, contamination and bowstringing.
- The vulva is situated adjacent to the groin creases and subject to constant movement when walking which contributes to the shear stresses associated with poor wound healing.
- The proximity of urine and faeces makes wound contamination inevitable and faecal and urinary diversion should be considered.
- Patients have frequently had previous radiotherapy and surgery leading to scarring and poor wound healing.
- The vulva is a dependant area that is prone to swelling and difficult to dress.
- Patients are often elderly and may be immunosuppressed due to comorbidities or medications.

4.2.1 Reconstructive surgical options

Secondary intention

If tension-free direct wound closure is not possible, smaller defects can be left to heal by secondary intention. This relies on the cooperation of the patient and the nursing staff to undertake regular dressing changes but can result in acceptable outcomes.

Split skin grafts

Skin grafts are usually taken from the buttock or thigh and rely on a healthy blood supply from the wound bed to ‘take’ and so are less reliable following radiotherapy or in a heavily scarred area. They do not provide any bulk and are often tight and unforgiving, which can be uncomfortable and can limit walking and sexual function.

Skin grafts are usually reserved for large areas when there are no flap options to provide adequate soft tissue cover.

Flap coverage

Flaps provide healthy vascularised tissue and do not rely on adequate perfusion from the wound bed to ‘take’ in the same way that skin grafts do. For this reason they are particularly useful in poorly vascularised areas such as in patients who have had radiotherapy to the vulva. Flaps are also thicker than split skin grafts and so give bulk that can be useful if radiotherapy is planned to the area, although they may be cumbersome and lead to discomfort.

Local flaps are taken from areas adjacent to the vulva, such as rhomboid flaps, lotus petal flaps or pudendal thigh flaps. They require less dissection to raise, but are smaller than distant flaps and there is a possibility that the blood supply to a local flap may have been compromised if there has been previous surgery to the region.

Distant flaps, such as the gracilis and rectus abdominis muscle flaps, provide a larger, more bulky reconstruction with a more predictable blood supply. However, the surgery is more complex with increased potential donor site morbidity.

C Plastic surgery involvement may be required for large defects and when radiotherapy has been used. The vulva is a challenging area for wound healing and faecal and urinary diversion is often required.

4.3 Surgical management of nonsquamous vulval cancer

Carcinoma of the Bartholin gland

This is a rare vulval cancer. Histologically, it is usually a squamous carcinoma or adenocarcinoma. The current evidence base is insufficient to suggest different management from squamous tumours. The lesions are often deep-seated or likely to be associated with metastatic disease. The close proximity to the anal sphincter may necessitate partial resection with reconstruction and this may necessitate a defunctioning temporary colostomy.[34,35] Any perimenopausal or postmenopausal woman with a persisting Bartholin abscess or cyst should be suspected of having a possible carcinoma. Appropriate biopsies and histological review should be undertaken. In general these cancers have a poorer prognosis than squamous cell carcinoma of the vulva and often multiple treatment modalities are required.

There are no data regarding the use of selective lymphadenectomy in Bartholin gland carcinoma. These patients will require bilateral inguinofemoral lymphadenectomy (because of the proximity of the gland to the midline).

Basal cell carcinoma and verrucous carcinoma

These squamous variants are rarely associated with lymph node metastases and can be managed by wide local excision. Basal cell carcinomas are also amenable to treatment by radiotherapy, which should be the preferred treatment if resection would compromise function (i.e. would cause sphincter damage).

Malignant melanoma

This group of tumours has not been shown to benefit from block dissection of the groin. Wide local excision is preferred. Relapse in this subgroup is high and closely correlates with the depth of invasion. On the vulva (which includes mucosal surfaces) Breslow's classification[36] is more appropriate than Clark's levels. As yet, there are no new strategies to minimise the risk of relapse in malignant melanomas.[37]

Recent evidence suggests there is an increased frequency of *KIT* mutations in vulval melanomas.[38] This may offer the possibility of entry into phase II clinical trials. All vulval melanomas should be discussed at the gynaecology specialist multidisciplinary team (MDT) and the specialist melanoma MDT. Centres should have effective and rapid channels of communication to facilitate inter-MDT discussion on the management of this rare subgroup of patients.

B Groin node dissection should be omitted in stage Ia squamous cancer, verrucous tumour, basal cell carcinoma and melanoma.

B Sentinel lymph node biopsy should be offered to all eligible women with squamous carcinoma of the vulva.

C Vulval melanomas need to be jointly managed with the appropriate melanoma MDT.

4.4 Morbidity related to surgery

The primary objectives of less radical surgery are to reduce morbidity while maintaining high cure rates for early vulval cancers. The complications associated with vulval and inguinal surgery are:

- wound breakdown
- wound infection
- deep vein thrombosis and pulmonary embolism
- pressure sores
- introital stenosis
- urinary incontinence
- rectocele
- faecal incontinence
- inguinal lymphocyst
- lymphoedema
- hernia
- psychosexual complications.

The risk factors for short- and long-term complications following surgery for vulval cancer have been described in a multivariate analysis on a cohort of 164 patients. Older age, diabetes, 'en bloc' surgery and greater drain production on the last day of drain placement were associated with a higher risk of short-term complications, while younger age and lymphocele were risk factors for long-term complications. However, the dissection of a greater number of lymph nodes was found to be protective against long-term complications.[39]

5. Radiotherapy

Clinical oncologists supervising treatment should have specific expertise in the management of gynaecological malignancies. They should manage integrated treatment plans involving radiotherapy with or without concurrent chemotherapy[40] (see section 6).

The factors influencing the need for adjuvant radiotherapy are surgical margins and groin node positivity. There is not enough evidence to recommend adjuvant local therapy routinely in patients with close surgical margins. Adjuvant treatment for positive margins has an improved survival compared with observation alone.[40]

Adjuvant radiotherapy should be considered when either groin has two or more lymph nodes involved with microscopic metastatic disease or there is complete replacement and/or extracapsular spread in any node.[41–44] There is no evidence to show whether adjuvant radiotherapy should be given to both sides or to the involved side only. Treatment should be to the groins and the pelvic nodes.

5.1 Primary treatment

Radiotherapy, with or without chemotherapy, is increasingly used in the management of advanced vulval cancer. Preoperative radiotherapy may allow for sphincter-preserving surgery. Radiotherapy may also be of use in place of surgery for histologically proven involved groin lymph nodes. It is unknown whether post-radiation groin node removal is advantageous in terms of outcome.

The scheduling of combined surgical and radiotherapeutic approaches needs to be individualised. While performing radiotherapy as the primary approach may result in the ability to avoid permanent functional damage,[44,45] surgery and subsequent healing may be compromised by the prior use of radiation. Furthermore, a temporary bowel diversion may be required for patients to be able to tolerate and complete a course of radiation therapy.

Treatment schedules

The majority of schedules are based upon those developed by the Toronto Group.[44] Fraction size is important, with 1.7 Gy being close to tolerance, although it is recognised that some centres may use slightly larger fractions (1.8 Gy). Doses will have to be reduced for radical treatment if fractions greater than 1.7 Gy are employed.

Radical treatment will usually require a prophylactic dose (45–50 Gy) to be delivered to the primary and nodal sites and the tumour is then boosted by a second phase of treatment by electrons, conformal radiotherapy or brachytherapy, to a total dose of 65 Gy. The total prescribed dose is determined by the clinical context.

A Cochrane review has suggested that there is no evidence that prophylactic groin irradiation should be used in preference to surgery.[45]

A Surgery is the cornerstone of therapy for the groin nodes in women with vulval cancer. Individual women who are not fit enough to withstand surgery, even when performed under regional anaesthesia, can be treated with primary radiotherapy.

6. Chemotherapy

Overview of chemotherapy for vulval cancer

Squamous cell carcinomas may arise in many primary sites and, in the majority of cases, those of the anogenital region share a common relationship to HPV infection. Squamous cancers of the vulva are uncommon and often occur in elderly unfit women; therefore there are few trials on which to base recommendations for chemotherapy treatment and most of what follows is drawn from observational studies of small series of patients.

Chemotherapy has been used neoadjuvantly to reduce the extent of surgery, and in the adjuvant setting, postoperatively, alone or concomitantly with radiation in node positive disease. Chemotherapy has also been used in recurrent and metastatic disease. Each of these treatment settings will be reviewed in turn.

6.1 Neoadjuvant chemotherapy for invasive squamous cell carcinoma

There are three small phase II trials and a number of case reports on the potential role of primary chemotherapy in patients with locally advanced vulval cancer deemed difficult to operate and requiring extensive surgery (Durrant et al.,[46] Benedetti-Panici et al.,[47] Geisler et al.,[48] Domingues et al.,[49] Tans et al.[50] and Narimatsu et al.[51]) All of the studies suggest that vulval cancer responds to chemotherapy to a variable extent and there is evidence that some cancers can be rendered more operable. Recurrence remains a problem, even after successful surgical removal of residual disease.

6.2 Adjuvant chemotherapy for vulval cancer

While radiotherapy has been the more usual adjuvant treatment and may benefit those at high risk of relapse,[52] only one feasibility study has focused on chemotherapy in this setting. Bellati et al.[53] looked at acute and long-term morbidity, recurrence rate and overall survival in 14 patients with multiple groin lymph node metastases, treated with postoperative cisplatin chemotherapy and no radiotherapy. All patients completed the treatment. At the time of reporting, 12 of the 14 women were still alive with a median follow-up of 57.5 months, a 3-year overall survival of 86% and a progression-free survival of 71%. They concluded that radical surgery followed by chemotherapy, in patients with multiple lymph node metastases, is a feasible strategy.

Ideally further studies, however, are necessary to compare adjuvant chemotherapy to radiotherapy, chemoradiation and best supportive care in patients affected by high-risk disease.

6.3 Chemotherapy for metastatic and recurrent vulval cancer

There are four small studies of chemotherapy for patients with advanced, recurrent or metastatic vulval carcinoma, not amenable to locoregional treatment. Chemotherapy has generally only been used in the salvage setting after surgery and/or radiotherapy, and the type of chemotherapy that was offered depended on the age, performance status and renal function of the patient.

Patients tend to be treated with similar chemotherapy agents, such as cisplatin, fluorouracil (5FU) and bleomycin, to those used in metastatic squamous cell cancers arising from other sites. Deppe et al.[54] performed the first study on the use of chemotherapy in recurrent vulval cancer. They treated four women with recurrent squamous cell carcinoma with Adriamycin in small doses at 3-week intervals. Three women experienced regression of nodal metastases and residual tumour; however the clinical benefit was unclear.

Mitoxantrone was assessed by the Gynecologic Oncology Group.[55] Nineteen patients with advanced vaginal and vulval cancer were treated with mitoxantrone at 3-weekly intervals. There were no responses to treatment and the median survival for the patients with advanced vulval cancer was 3.2 months. It was thus concluded that mitoxantrone displays no activity in patients with advanced carcinoma of the vulva.

In an EORTC (European Organisation for Research and Treatment of Cancer) phase II trial, Witteveen et al.[56] analysed the use of 3-weekly paclitaxel in patients with recurrent, metastatic or locally advanced vulval cancer not amenable to surgery or radiotherapy. Thirty-one women were included, of whom 29 were assessable for response. Women in the study received a median of four cycles, with an overall response of 13.8% with two complete responses. The median follow-up was 24 months and median progression-free survival was 2.6 months.

Cormio et al.[57] evaluated the activity and toxicity of a combined regimen of cisplatin (day 1) and vinorelbine (day 1, day 8) in 16 women with recurrent vulval carcinoma. None had previously been treated with chemotherapy and the median age was 65 years. Nine women had previously received radiotherapy. The recurrence was local (perineum, vagina and/or vulva) in nine women whereas seven had recurrent groin lymph nodes metastases. Responses were recorded in six women (40%), of whom four (27%) achieved a complete remission and two (13%) had a partial response; another four women (27%) had stable disease and five had progressive disease. The overall survival was 19 months.

6.4 Concomitant chemotherapy and radiotherapy

Chemotherapy used concomitantly with radiation (chemo-RT) should be considered analogous to use in cervical cancer and either cisplatin alone or cisplatin plus fluorouracil should be considered. If used alone, cisplatin at 40 mg/m^2 weekly, concomitantly with radiotherapy, would be advised. Alternative regimens may include cisplatin and fluorouracil using the regimen above, or platinum, mitomycin C and bleomycin given on week 1 and week 4 of a prolonged course of radiation. This should be managed by a unit experienced in looking after women with vulval cancer, as reactions and toxicity can be quite significant. Women should be referred to their regional centres where gynaecological surgeons and oncologists work closely in teams. There is some anecdotal evidence that chemo-RT increases skin toxicity and pelvic morbidity.

6.5 Future developments

At present both erlotinib and cetuximab are used in a variety of other squamous cell cancers, e.g. head and neck, and lung, with the aid of mutation analysis to try and target which patients would benefit from these additional therapies. It may very well be that with time, these two drugs, among other biological agents, will prove very useful in women not fit for aggressive chemotherapy in vulval cancer.

C Primary and recurrent vulval cancer does respond to chemotherapy but responses are variable and toxicity may be a problem in this population of patients.

C Future development of targeted therapy with drugs such as erlotinib through mutation testing may lead to improvement in vulval cancer treatment toxicity benefit ratio and provide effective systemic treatment even for the more infirm patients.

7. Treatment of recurrent disease

7.1 Recurrence rates and survival

Recurrence rates for invasive squamous cell carcinoma range from 15% to 33%. In a review of the literature, the vulva was found to be the most common site of recurrence (69.5%) with the groin nodes affected in 24.3%, the pelvis in 15.6% and distant metastases in 18.5%.[58]

Survival following regional recurrence is poor so all attempts to prevent it must be made at the time of primary treatment. However, the outcome from local recurrence in vulval cancer is better than that of other gynaecological cancers. Skin bridge recurrence has been reported to be more likely to occur in patients with positive lymph nodes.[59] If the nodes are known or suspected to be positive at the time of primary treatment, an en bloc dissection should be considered to remove the tissue between the vulva and involved nodes.

Clinical oncologists and gynaecological surgeons need to work closely together to manage patients with recurrent disease, which can be challenging. Integrating all treatment modalities (surgery, chemotherapy and radiation) can, however, be highly rewarding.

Treatment and outcome depend on the site and extent of the recurrence.[58] Surgical treatment of the recurrence can result in a 5-year survival rate of 45%, although the prognosis is worse for groin dissection and for women in whom only a biopsy is taken.[60] If excision would impair sphincter function, irradiation should be considered as the first choice. If irradiation has already been given to maximum dose, then excision should be considered. Such cases require careful joint planning with clinical oncologists and plastic and reconstructive surgeons experienced in the treatment of vulval disease.

7.2 Groin recurrence

Groin recurrence has a much poorer prognosis and is difficult to manage. In women who have not been treated previously with groin irradiation, radiotherapy (with or without additional surgery) would be the preferred option. The options are much more limited in those who have already been irradiated and palliation, which may include surgery, should be considered. In women who have had both surgery and radiotherapy to the groins, the palliative care team should become involved soon after the confirmation of groin recurrence.

7.3 Chemotherapy for relapsed disease

Chemotherapy for recurrent disease may be determined by what previous treatments have been offered and also by the age and performance status of the patient. The use of chemotherapy in this context is addressed in section 6.3.

One challenge is that many of these patients are relatively elderly and therefore not good candidates for aggressive novel combinations and this, taken together with their relative rarity, makes clinical trials difficult to perform. Collaboration between the regional UK centres, either through the National Cancer Research Institute or through groups such as the EORTC or the Gynaecological Cancer Group, should be encouraged.

8. Follow-up

The follow-up of most cancers, including vulval cancer, is based on custom and practice and not evidence. Up to a third of vulval cancers will recur even after satisfactory primary treatment. As salvage is largely dependent on either further excision or radiotherapy, recognition of recurrence as early as possible seems logical. For this reason, most centres would adopt a follow-up regimen of every 3 months for the first year, 6-monthly for the second year and yearly thereafter. There are no data to support this approach.

Late recurrence is unusual but is encountered so follow-up may be required for many years. In addition, patients should be advised to bring forward their review if they experience any new symptoms or if the appearances of the residual tissues change in any way. It should be remembered that elderly and frail patients may find self-examination difficult.

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Appendix I. International Federation of Gynecology and Obstetrics (FIGO) staging system

Stage I	**Tumour confined to the vulva**
Stage Ia	Lesions ≤ 2 cm in size, confined to the vulva or perineum and with stromal invasion ≤ 1 mm. No nodal metastasis
Stage Ib	Lesions > 2 cm in size or with stromal invasion > 1 mm confined to the vulva or perineum. No nodal metastasis
Stage II	**Tumour of any size with extension to adjacent perineal structures (lower 1/3 urethra; lower 1/3 vagina; anus) with negative nodes**
Stage III	**Tumour of any size with or without extension to adjacent perineal structures (lower 1/3 urethra; lower 1/3 vagina; anus) with positive inguinofemoral nodes**
Stage IIIa	(i) With 1 lymph node metastasis (≥ 5 mm), or (ii) 1–2 lymph node metastasis(es) (< 5 mm)
Stage IIIb	(i) With 2 or more lymph node metastases (≥ 5 mm), or (ii) 3 or more lymph node metastases (< 5 mm)
Stage IIIc	With positive nodes with extracapsular spread
Stage IV	**Tumour invades other regional (upper 2/3 urethra; 2/3 vagina) or distant structures**
Stage 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.
Stage IVb	Any distant metastasis including pelvic lymph nodes