British Gynaecological Cancer Society (BGCS) Vulval Cancer Guidelines: Recommendations for Practice

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The purpose of this guideline is to collate evidence and propose evidence-based guidelines for the diagnosis and management of adult patients with vulva carcinoma treated in the UK. Malignant melanoma may present via similar routes and will be discussed. The reader is referred to the Ano-uro-genital Mucosal Melanoma Full Guideline (1) for more detailed recommendations. The management of vulval sarcoma is outside of the scope of this guideline.

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Table of Contents

1 Introduction

1.1 Grades of recommendations

Recommendations are graded as per the Royal College of Obstetricians and Gynaecologists document. Clinical Governance Advice No. 1: Guidance for the Development of RCOG Green-top Guidelines, available on the RCOG website at:

https://www.rcog.org.uk/en/guidelines-research-services/guidelines/clinical-governance-advice-1a/.

Evidence was searched in the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library 2014, Issue 12), MEDLINE and EMBASE up to April 2018, registers of clinical trials, abstracts of scientific meetings, reference lists of included studies and contacted experts in the field.

1.2 Guidelines development process

The guideline development process is detailed below:

- Chair, officers, council and guidelines committee (GC) nominated a lead for each guideline topic;
- Lead then identified a team called the guideline team (GT) to develop the 1st draft;
- 1st draft was submitted to the GC;
- GC approved draft and recommended changes;
- Changes were accepted by the GT who produced the guidelines;
- 2nd draft was then submitted to council members and officers;
- Council and officers approved 2nd draft and recommended changes;
- Changes were then accepted by GC and GT;
- 3rd draft was sent to national and international peer review;
- GC and GT then made changes based on peer review comments;
- 4th draft was sent back to council for approval;
- 4th draft was sent to BGCS members for feedback;
- GC and GT then made changes based on members' feedback;
- 5th draft was sent to public consultation including patient support groups;
- GC and GT then made changes based on non-members' feedback;
- Final draft approved by council and officers.

2 Background and epidemiology

Vulval cancer is a rare disease with 1,300 new cases registered in the UK during 2015, representing less than 1% of all new cancer cases registered that year. In the UK it is the 20th most common female cancer and 4th most common gynaecological cancer, with a crude incidence rate of 3.9/100 000. (2) Incidence in the UK is highest in females over 90 years of age. The Incidence of vulval cancer has increased by 18% since the early 1990s, mainly due to an increase in incidence of over 50% in those under 60 years. (3) While most vulval cancer is still diagnosed in women aged over 70 years, age standardized rates have increased by 92% within the 50-59 cohort between 1993-1995 and 2012-2014. This increase in incidence in younger cohorts is most likely due to an increase in human papilloma virus (HPV)-related VIN within those groups. (3) However, Dutch Registry data demonstrate an almost two-fold rise in incidence of lichen sclerosus between 1991 and 2011, so the rise may not be solely HPV-related. (4)

Approximately 90% of vulval cancers are squamous cell carcinomas, with the main risk factors for disease being infection with high risk HPV and inflammation due to vulval dermatoses, such as lichen sclerosus and lichen planus. The remaining 10% are made up of primary vulval melanoma, basal cell carcinoma, Bartholin's gland carcinoma, adenocarcinoma, and rarely, sarcoma.

In 2014 there were 450 vulval cancer-related deaths in the UK, representing less than 1% of all cancer-related deaths in females that year. The mortality rate increases with age with the majority of deaths occurring in women over 70 years of age. However, mortality rates in this group have reduced by 30% since the early 1990s. (5)

The increased incidence of squamous cell vulval cancer is mirrored by data from Germany and Australia, where rates have nearly doubled in the past decade. (6, 7) It is likely to be decades before the effects of HPV vaccination on reducing vulval cancer are known; nevertheless, it is anticipated that a decrease will occur, as HPV16 is the most common viral subtype associated with vulval cancer. Unfortunately, this is likely to be less dramatic than for other HPV-related malignancies, as vulval dermatoses account for a large proportion of vulval cancers.

3 Prevention, screening, presentation and diagnosis

3.1 Prevention and treatment of pre-disposing conditions

For a summary of recommendations on prevention, screening, please see Table 1. The most common type of vulval cancer is squamous cell carcinoma (VSCC). This may be HPV-independent, developing on a background of vulval dermatoses (lichen sclerosus and lichen planus) and differentiated vulval intraepithelial neoplasia (dVIN) or it may HPV-dependent with a background of usual type vulval intraepithelial neoplasia (uVIN). The combination of the two may increase the risk as the risk of developing VSCC in women with VIN *and* LS was 19% in one Dutch cohort study over 10 years. (4)

3.1.1 HPV-related squamous cell carcinoma

HPV Vaccination

The majority of HPV-related VSCC is caused by HPV16. (7) HPV vaccination will likely provide significant protection to those vaccinated prior to HPV exposure. However, since the natural history of developing VIN and vulval carcinoma is often decades from original exposure, the effects of HPV vaccination programmes are likely to take many years to become apparent. HPV vaccination has already had a significant effect on rates of genital warts and cervical intraepithelial neoplasia in vaccinated populations. (8) The time to development from exposure is much lower for benign warts than for usual type vulval intraepithelial neoplasia (uVIN), the pre-malignant lesion for HPV-related VSCC, so these benefits will take longer to realise.

Prophylactic vaccination against HPV6, 11, 16 and 18 has been shown to result in a substantial decrease in the development of preinvasive vulval lesions and it is anticipated that the relative proportions of HPV- and non-HPV-associated malignancy may alter as vaccine coverage increases and with the use of vaccines protecting against additional HPV types. (9) Studies are ongoing to determine whether HPV-vaccination following diagnosis of uVIN can reduce the risk of recurrence or development of SCC. (7) Studies looking at the effect of HPV vaccination on development of CIN in those already exposed to HPV did not suggest a significant benefit overall in the incidence of CIN2+. (10) In contrast, retrospective subgroup analysis of a randomised control trial (RCT) of HPV vaccination demonstrated a 46.2% reduction in incidence of further HPV-related disease (95% confidence interval 22.5% to 63.2%) in those vaccinated prior to initial treatment for HPV-related disease, compared to the unvaccinated cohort. (11) Other studies suggest that HPV vaccination after treatment for CIN may reduce the risk of recurrence and other HPV-related disease (12) and RCTs to look at this specifically are on-going.

Treatment of uVIN

A systematic review of the natural history of VIN3 found 97 articles including a total of 3,322 women. There was an occult cancer rate of 3.2% in those with suspected VIN3 and 3.3% went on to develop VSCC during follow up. (13) Of 88 women with untreated VIN3, 9% went on to develop VSCC over 12 to 96 months. However, they concluded that the progression rate to VSCC is likely to be over-estimated.

A Cochrane review of intervention for treatment of uVIN examined effects of imiquimod, cidofovir, indole-3 carbinol and surgery. (14) They found that topical imiquimod, an immune modulator was more effective than placebo in achieving a response (complete or partial) to treatment 5-6 months after randomisation (risk ratio (RR) 11.95, 95% confidence interval (CI) 3.21 to 44.51; high-certainty evidence). A complete response occurred in 58% of women in the imiquimod groups and none in the placebo groups (RR 14.40, 95% CI 2.97 to 69.80). Persistent responses after 12 months were present in just over a third of women. Only one study reported vulval cancer rates at 12 months follow up (1/24 and 2/23 in imiquimod and placebo groups, respectively). Adverse events were more common with imiquimod than placebo (RR 7.77, 95% CI 1.61 to 37.36; high-certainty evidence). One very small, long-term follow-up study of those with complete response to imiquimod demonstrated very low recurrence rates of uVIN. (15)

Complete response rates after 6 months were similar for a 16-week course of imiquimod and cidofovir (imiquimod 45% and cidofovir 46%; RR 1.00, 95% CI 0.73 to 1.37; moderate-certainty evidence). A follow up study found that responses for complete responders were maintained after 18 months, especially in the cidofovir group (94% for cidofovir (95% CI 78.2-98.5) versus 71.6% for imiquimod (95%

CI 52.0-84.3)). (16) Side effects, mainly headache, fatigue and discontinuation due to pain, were slightly more common with imiquimod than cidofovir. Cidofovir cream is currently not licenced for use in uVIN.

The same Cochrane review looked at evidence for surgical treatment of uVIN and found low-quality evidence from the better studies where data were adjusted for confounders. (14) There was little or no difference in the risk of VIN recurrence between surgical excision and laser vaporisation (51% (37/70) of women overall, at a median of 14 months). Recurrence was, unsurprisingly, more common in those with multifocal uVIN (66% versus 34%). There was only very low-certainty evidence for other treatments such as photodynamic therapy, Cavitron ultrasonic surgical aspiration and loop electrosurgical excision.

In the small surgical studies included in the Cochrane review, vulval cancer occurred in 11 women (15.1%) overall at a median of 71.5 months (9 to 259 months). They concluded that, if cancer is suspected, despite a biopsy showing uVIN only, 'surgical excision remains the treatment of choice'. However, if an occult cancer was not suspected, treatment of uVIN can be individualised, taking into account women's preferences and the site and extent of disease, using a combination approach to optimise outcomes, which can include conservative treatment and close follow up with vulvoscopy in selected patients. It should be emphasised that the volume of data in this area, as with much of the vulval field, is limited.

3.1.2 Squamous cell carcinoma on a background of lichen sclerosus (LS)/lichen planus (LP)

Lichen sclerosus is associated with an increased lifetime risk of developing vulval cancer, with estimates of the risk varying between 2.6- 6.6%. (4, 17) However, these data are not based on population-level data and lichen sclerosus is under diagnosed, so these data are likely to be at high risk of bias and are likely to over-estimate the risk. Data from non-randomised studies suggest that good control of LS/LP with ultra-potent topical steroids (such as Clobetasol 17- propionate 0.05%) may reduce the risk of progression to SCC. (17-19) There are yet no RCT level data to support this, although control of active LS/LP should be recommended to improve symptoms, reduce scarring and may reduce the risk of developing malignancy. Often women are fearful of using 'too much' steroid cream and they should be reassured that appropriate usage (less than 30 g tube of ultra-potent steroid ointment/cream, such as Dermovate (clobetasol propionate 0.05%), over a 3-month period) is unlikely to be harmful and may be of benefit, both to scarring/vulval appearance as well as longer term risk of cancer. For the same reasons, women should be advised to avoid irritants that can exacerbate LS/LP, particularly detergents, such as soap.

3.1.3 Mucosal malignant melanoma

Unlike cutaneous melanomas, vulval mucosal melanomas are not related to ultraviolet light exposure. A small minority may be related to c-kit mutations, which are more common than in cutaneous melanoma. (20)

3.2 Screening

There are currently no proven screening tests for vulval carcinoma.

Those with known VIN and lichen sclerosus/lichen planus are at higher risk. Rates of progression to vulval carcinoma were 5.7% in a 14-year series for uVIN (21) and a 2.6- 6.6% overall risk for those with lichen sclerosus/lichen planus (17, 22), increased significantly when associated uVIN. (4) However, differentiated VIN (dVIN), which arises on a background of lichen sclerosus, has a very high risk of progression to cancer compared to uVIN and should ideally be surgically excised (relative risk (RR) of progression: dVIN RR= 38.5 (9.8-150.8); uVIN = 0.065 (0.03-0.15). (23, 24) Current guidelines from the

British Association of Dermatologists recommend annual review in primary care in those with lichen sclerosus, following review at 3-months to check response to initial treatment and a 6-month follow up to check compliance and understanding of self-management. (25) Importantly, patients should be aware of the small risk of developing vulval cancer and report new lesions to their GP, especially if these symptomatic. Recent data suggest that the risk of vulval cancer in the presence of a lesion is around 13% and presence of a suspicious vulval lesion should prompt rapid 'Cancer Wait Time' referral to secondary care. (26, 27)

Women with uVIN should receive follow up with formal vulvoscopy. These women are at increased risk of multi-focal disease, so it is important to ensure that they have appropriate follow up with timely cervical screening. Patients are also at risk of anal/peri-anal intraepithelial neoplasia and those affected may need a multi-disciplinary approach to follow up and management.

Those with multi-focal disease should be followed up in colposcopy by someone experienced in treatment for CIN and uVIN, although the NHS Cervical Screening Programme guidelines do not specify a frequency for follow up. (28) The risk of recurrent disease is high, particularly in the first two years. (29) Follow-up regimens should reflect this fact, with increased surveillance in the first two years, particularly for those with multifocal disease. Recommended minimum follow-up intervals after successful treatment would be six-monthly in the first two years and annual follow-up to 5 years. Patients with unifocal, treated disease may be discharged at that time, with instructions to return if new lesions or symptoms develop. Patients with multifocal or recurrent disease may require more long-term follow-up. HIV testing should be considered as per the 2008 recommendations from the British HIV Association, British Association of Sexual Health and HIV British Infection Society (https://www.bashhguidelines.org/media/1067/1838.pdf).

The effectiveness of anal screening in this population has not been proven and most data on anoscopy and anal cytology is limited to higher risk populations (Human Immunodeficiency Virus-positive (HIV+) men who have sex with men (MSM)), reviewed in (30). An expert review group of American Society Colposcopists and Cervical Pathologists and the International Anal Neoplasia Society examined the data and made recommendations on anal HPV infection, anal intraepithelial neoplasia (AIN) and anal cancer in women. They did not find data to support routine anal cytology or anoscopy in women with uVIN or vulval cancer, although noting that they were at higher risk than the general population. (31) They recommended screening for anal cancer with digital ano-rectal examination and assessment if anal cancer symptoms developed, such as pain or bleeding. They noted that routine screening and treatment of AIN2/3 was not proven to be effective in reducing anal cancer in this population.

Recommendation	Grade of recommendation
HPV vaccination is likely to reduce the incidence of uVIN and HPV-related vulval SCC in the future.	Grade C
Imiquimod, Cidofovir and surgical excision are treatment options for high grade VIN all with ~50% response/recurrence rates by 12 months' post-treatment. However, cidofovir is currently unlicensed for use in uVIN.	Grade A
Good control of lichen planus and lichen sclerosus with ultra-potent topical steroids improves symptom and may reduce the incidence of developing SCC.	Grade C
There is currently no proven screening test to prevent vulval cancer.	Grade D

Recommendation	Grade of recommendation
Women with multi-focal HPV related disease should be followed up colposcopy of the lower genital tract and digital ano-rectal examination with prompt referral should symptoms of anal cancer develop.	Grade D
Women with multi-focal HPV-related disease should be offered HIV testing.	Grade D
Women with high grade uVIN should be followed up with careful clinical inspection +/-vulvoscopy.	Grade D
Women with uncomplicated lichen sclerosus or lichen planus can be followed up in primary care and once quiescent and confident of self-management, 12-monthly review is suggested.	Grade C
Women with lichen sclerosus who develop new lesions should be referred to secondary care, via a Cancer Wait Pathway, if these do not respond to nightly ultra-high potency steroids within 1-2 weeks.	Grade C

Table 1. Recommendations for prevention and screening

3.3 Presentation

For recommendations on presentation and diagnosis, see Figure 1 and Table 2. Most vulval carcinomas will present with a specific lesion. The risk of cancer, in the presence of a 'suspicious vulval lesion', was 12.8% in a recent study of women referred to a secondary care 'rapid access clinic' with vulval symptoms. (26) This risk of invasion was higher, if the lesion was symptomatic (pain and/or bleeding). Women with generalized vulval irritation without a visible lesion on careful examination, were extremely unlikely to have a cancer diagnosis.

Women with clinical features highly suspicious of vulval cancer, for example a fungating lesion +/- palpable groin nodes, should be referred to a cancer centre without the need to await biopsy results. Punch biopsies may not adequately sample the lesion, especially if it is large and/or deep, and delay for diagnostic biopsy is not warranted.

Vulval melanoma is rare, presents as a vulval lesion, which may or not be pigmented and may or may not develop in the background of melanocytic dysplasia. Symptoms may include altered vulvo-vaginal pigmentation, itching or bleeding. Alternatively, an asymptomatic lesion is noted, which may occur as an irregularly outlined pigmented or non-pigmented macule, papule, patch or nodule with or without ulceration. Some lesions will be found on clinical examination after noticing groin lymph node(s) enlargement.

Basal cell carcinoma of the vulva tends to present with a discrete vulval lesion or classical raised, rolled-edge ulcer, without a background dermatosis or evidence of uVIN.

Bartholin's gland carcinoma is rare and may present with a mass in the vulva/lower vagina over the area of the Bartholin's gland. These lesions are often painful and may be mis-diagnosed as a Bartholin's cyst or abscess. The diagnosis should be suspected and excluded in those aged over 40 years presenting with a 'Bartholin's abscess', since inadvertent Bartholin's gland 'excision' or marsupilisation can delay diagnosis and/or make further surgical treatment more challenging.

3.4 Diagnosis

Incisional biopsy (punch or wedge biopsy) ideally including the edge of a lesion, where there is a transition from normal to abnormal tissues. Biopsies should avoid a central ulcer, since this may not be diagnostic. Biopsies should be of adequate depth to allow differentiation between superficially invasive and those with invasion > 1 mm, since this will inform subsequent management.

Excision biopsy should be avoided, where possible, since this can limit options for more conservative treatment with wide local excision and sentinel node biopsy. This is especially the case, if the lesion is small, as the vulva can heal well and the original site be hard to determine at the time of more definitive treatment. However, there may be exceptions to this, for instance in someone who is very elderly or frail it may be acceptable to excise a small, symptomatic lesion under local anaesthetic for palliation and planning of subsequent treatment. This should ideally be performed by the gynaecological oncologist who will perform subsequent treatment. Histological confirmation is required prior to consideration and planning more radical treatment.

At a minimum, a detailed diagram of the vulva, indicating each biopsy site, should be drawn. Use of a schematic diagram, which can be annotated is encouraged (e.g. https://www.nva.org/what-is-vulvodynia/vulvar-anatomy/). Ideally, vulvoscopic 'before and after' biopsy photos should be taken (with a scale indication). This will help to localize the lesion for the treating gynaecological oncologist and assist pre-planning of more definitive treatment. GMC and local guidance on the capture and storage of imaged should be followed. If more than one lesion is present, each individual biopsy should be sampled separately, sent in separate pots and carefully labelled, so that lesion site can be identified at a later date.

Recommendation	Grade of recommendation
Women with suspicious vulval lesions should be referred to a rapid access clinic for urgent assessment, as per NICE guidelines. (169)	Grade C
Women highly likely to have vulval cancer on clinical grounds should be referred to a gynaecological cancer centre without waiting for biopsy results.	Grade D
Clear documentation of clinical exam size of lesion, distance to the midline/clitoris/anus/vagina/urethra and palpation of lymph nodes is mandatory. Imaging, with indication of biopsy sites and/or clinical drawing is essential for further treatment planning.	Grade D
Suspicious vulval lesions should ideally be sampled with a punch or wedge biopsy and excisional biopsy avoided until a diagnosis is made.	Grade D
Biopsies should include the edge of a lesion to ascertain the background condition.	Grade D
At a minimum, a detailed diagram, indicating lesion and biopsy sites, should be drawn.	Grade D
Ideally, clinical photographs, before and after biopsy should be taken, with an indication of scale.	Grade D
Biopsies from separate lesions should be sent in separate pots and clearly labelled.	Grade D

All cases vulval cancer should have diagnosis confirmed by a specialist multi-disciplinary team (MDT) prior to planning radical treatment.	Grade D

Table 2. Recommendations for presentation and diagnosis

Vulval lesion
(+/- symptoms of pain/bleeding irritation)

High suspicion of malignancy

Low suspicion of malignancy

Wedge biopsy,
photos +/- diagram
indicating biopsy site

Clinically LSA/LP

Clinically VIN
(uVIN or
dVIN)

Clinically
benign

Refer to gynae oncology team.
**Do not perform excision
biopsy or wait for biopsy
results**

Clinical photos
for later
comparison.
Treat with
nightly ultra
high potency
topical steroids

Reassure
and D/C to
primary care

No improvement
after 2 weeks (or
treated adequately
prior to referral)

Punch or wedge biopsy, including
lesion margin, photos +/- diagram
indicating biopsy site. **Do not
perform excision biopsy without
histology, as may rule out option
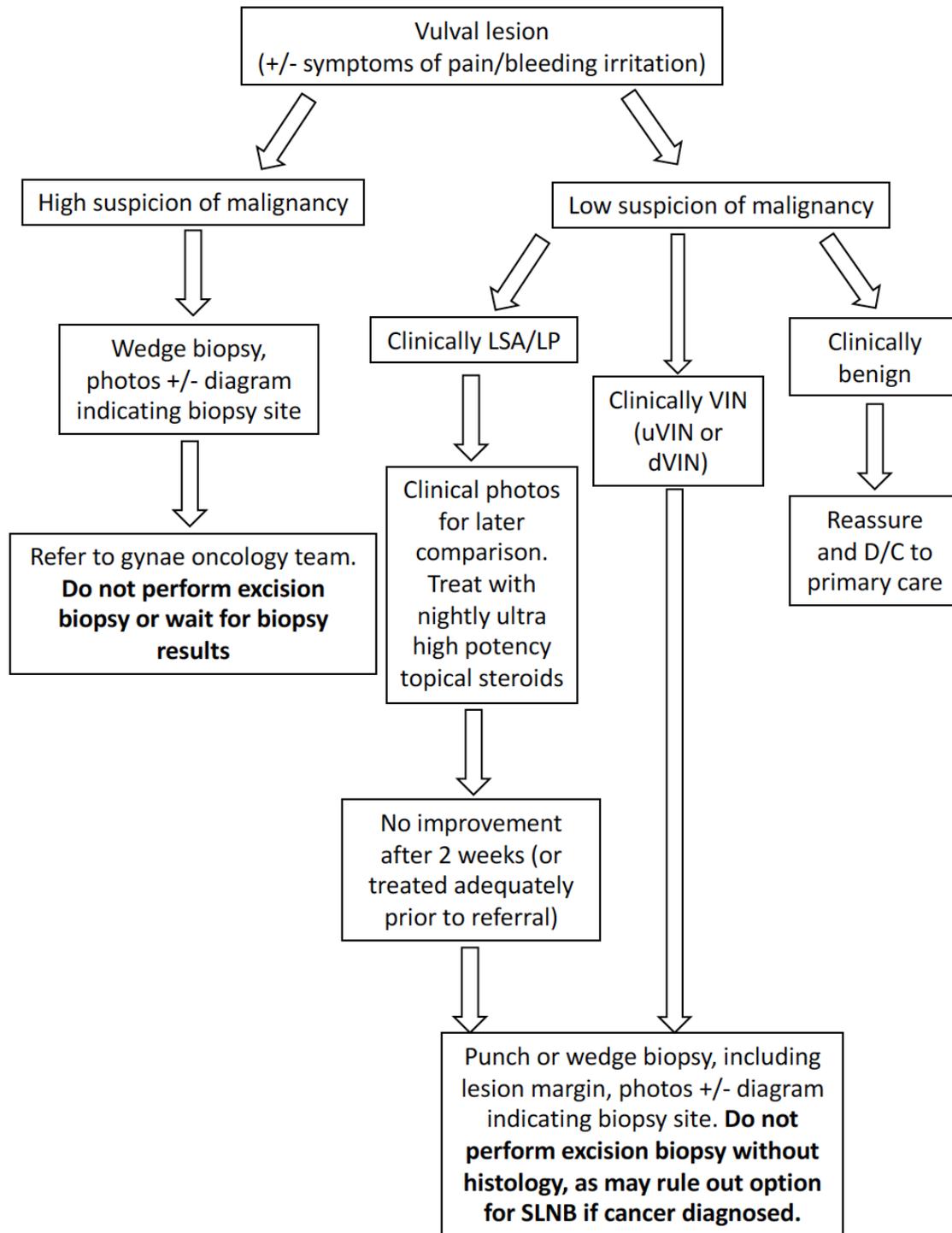for SLNB if cancer diagnosed.**

Figure 1. Flowchart demonstrating investigation of suspicious vulval lesion. LSA= Lichen Sclerosus Atrophicus; LP = Lichen Planus; VIN = vulval intraepithelial neoplasia; uVIN = usual-type VIN; dVIN = differentiated VIN; D/C = discharge

3.5 Pre-operative investigations

For recommendation on pre-operative investigations, see Table 3.

3.5.1 Squamous Cell Carcinoma (SCC)

Squamous cell carcinoma most commonly spreads via inguinal lymph nodes and rarely presents at distant sites, if regional nodes are negative. Imaging is poor at excluding microscopic groin node metastases, hence groin node surgery is recommended for those with greater than FIGO Stage Ia SCC. Prior to sentinel lymph node (SLN) biopsy, clinical examination and imaging of the groins are required to identify metastatic disease, since obvious groin node involvement would be a contraindication to SLN biopsy. The groins can be assessed with ultrasound, but cross-sectional imaging (with computerised tomography of chest, abdomen and pelvis (CT CAP), or magnetic resonance imaging (MRI)), will provide additional information on the presence of pelvic lymphadenopathy and distant disease and should be employed prior to lymphadenectomy. If radical surgery is proposed, there may be a role for positron emission tomography CT (PET-CT).

Those with suspicious groin nodes on clinical examination and/or imaging may be further investigated with USS-guided fine needle aspiration (FNA) or core biopsy, where node positivity would change management. Evaluation of the pelvic nodes with cross sectional imaging (MRI or CT) is recommended before undertaking lymphadenectomy. Staging with full body, cross-sectional imaging (CT CAP) should be considered for all those diagnosed with more than minimally invasive disease, as the presence of distant metastatic disease will influence the extent of loco-regional treatment options. MRI (pelvis) can be used for further assessment of the loco-regional disease, if locally extensive. CT is also suggested for those who are not fit for radical treatment, to aid discussion and planning of treatment options. (32)

3.5.2 Melanoma

Vulval melanoma commonly presents with a more locally advanced lesion than cutaneous melanoma, since the area is difficult to visualise. The risk of metastatic disease (both lymphatic and haematogenous spread) is high. Recommended imaging at diagnosis would include CT CAP and also CT or MRI head, since systemic disease and intra-cranial lesions are not uncommon. Please see the Ano-uro-genital Mucosal Melanoma Full Guideline for further details. (1)

3.5.3 Basal Cell Carcinoma

Distant disease spread is rare and no specific imaging is required, unless there is clinical suspicion of nodal disease.

3.5.4 Bartholin's Gland Carcinoma

Bartholin's gland carcinoma may present with more advanced disease, since they arise deep to the surface of the skin and are less clinically obvious. Pre-operative imaging with CT CAP is therefore recommended, since these lesions are not suitable for a SLN approach and there is an increased risk of locoregional spread at diagnosis. MRI pelvis may help to delineate the local degree of involvement.

3.5.5 Paget's disease of the vulva

See section 5.1.2 for discussion of management of Paget's disease of the vulva, including pre-operative investigations.

Recommendation	Grade of recommendation
Gross nodal involvement should be excluded by clinical examination and appropriate imaging / radiologic staging.	Grade D
If sentinel lymph node biopsy is considered, imaging of the groins either by ultrasound, CT, or MRI is suggested to identify potential lymph node metastases.	Grade D
FNA or core biopsy can be used to evaluate suspicious nodes when this would alter primary treatment, although removal of involved lymph nodes should be considered standard of care.	Grade D
Further staging with CT/PET-CT is recommended in the presence of proven metastatic disease (i.e. positive lymph nodes) and/or in advanced disease prior to radical treatment/surgery.	Grade D
No additional imaging is required in the preop assessment of BCC lesions, unless there is a clinical suspicion of nodal disease.	Grade D
Melanoma and Bartholin's cancers should be assessed with combination imaging (MRI and CT) to provide information on the extent of local disease and metastatic disease. PET-CT may be appropriate in selected cases.	Grade D

Table 3. Recommendations for pre-operative investigations

4 Pathology

For a summary of pathological subtypes, please see Table 4.

4.1 Precursor lesions

4.1.1 Usual/classical VIN (HPV-associated neoplasia)

The nomenclature of precursor lesions in HPV-related neoplasia is varied and includes the terms usual type VIN and classical VIN. The terminology recommended by the World Health Organisation (WHO) and ISSVD refers to LSIL (low-grade squamous intraepithelial lesion that includes HPV-related changes and VIN1) and HSIL (high-grade squamous intraepithelial lesion, which encompasses VIN2, VIN3). (33) The terms LSIL and HSIL are not widely used in the UK and the use of the alternative terms low- and high-grade VIN can be used with sub-categorisation as VIN2 or VIN3. This lesion is characterized by cytological atypia, mitoses extending beyond middle thirds of the epithelium and lack of maturity of the squamous cells with or without associated stigmata of HPV infection such as koilocytosis.

4.1.2 Differentiated VIN

This is an HPV independent lesion that is often seen in older women on a background of lichen sclerosus. It is characterised by basal cell atypia and abnormal keratinocyte differentiation. Differentiated VIN is typically associated with p53 mutations.

4.1.3   Other putative precursors

Vulvar acanthosis with altered differentiation (VAAD) is a non-invasive squamous proliferation that maybe a precursor to verrucous carcinoma. (34)

4.2 Pathology of squamous cell carcinoma

4.2.1   Types of squamous cell carcinomas

Invasive squamous cell carcinomas of usual type constitute 90% of vulvar cancers. Two pathogenetic pathways exist and correlate with the precursor lesions: an HPV-related pathway which is associated with younger age, HPV infection, uVIN and smoking; and a p53-related pathway that is associated with older age of onset, dVIN and lichen sclerosus.

Verrucous carcinomas are rare, highly differentiated squamous cell carcinomas that are unrelated to both HPV and p53 mutations.

4.2.2   Macroscopic features of importance

Documentation of specimen size allows correlation between clinical appearances of the specimen. Measurement of the tumour and distance from resection margins is important, as size is included in FIGO and TNM staging. (35, 36)

4.2.3   Microscopic features of importance

Grading

Squamous carcinomas are graded as well differentiated (grade 1), moderately differentiated (grade 2) and poorly differentiated (grade 3) according to the degree of keratinisation, intercellular bridges and pleomorphism. (36) There is no agreed grading system for adenocarcinoma of the vulva.

Grade or differentiation in squamous cell carcinoma has been shown to be linked to five-year survival rates. (37)

Depth of invasion

This is an independent prognostic factor. It is especially important to measure depth of invasion whenever possible as FIGO staging uses this measurement to distinguish between stage Ia and stage Ib tumours.   Reference to the vulvar cancer dataset of the Royal College of Pathologists is recommended for further details. (36)

Lymphovascular and/or perineural invasion (PNI)

Both factors are associated with higher risk of recurrence. Presence of malignant cells in the layers of the nerve sheath is associated with a worse prognosis. (38)

Clearance margin

This is discussed in section 5.1.1.

Preoneoplastic and non-neoplastic disease

Presence of lichen sclerosus and differentiated VIN at excision margins are associated with increased risk of local recurrence. (39, 40)

p16/p53 status

It is increasingly recognised that HPV-associated squamous carcinomas have better outcomes than HPV-independent cancers. Block positive p16 staining is a surrogate marker of HPV aetiology and is recommended on all vulval squamous cell carcinomas. (41, 42)

4.3 Spread

4.3.1   Lymph node metastasis

The number of involved lymph nodes, the size of the largest metastatic deposit and the presence or absence of extranodal spread should be recorded. Nodal deposits greater than 5 mm in size have been shown to correlate with poorer survival. In sentinel nodes, it is important to document the size of nodal metastases, even if they are less than 5 mm. (43)

4.3.2   Sentinel lymph nodes (SLN)

A sentinel node can be defined as any lymph node receiving drainage directly from the primary tumour. The indications and evidence for sentinel lymph node biopsy are discussed in section 5.1.3. (44) Intraoperative frozen sectioning of lymph nodes may lead to tissue loss and therefore examination of paraffin-embedded tissue is recommended. All nodal tissue is sampled. The technique is described in detail in the British Association of Gynaecological Pathologists document on protocols for processing of sentinel lymph nodes. (https://www.thebagp.org/download/bagp-sentinel-node-protocol/) (36)

Definitions of nodal involvement

The size of the metastases in the lymph node affects the stage allocated. These are defined as:
Macrometastasis: >2 mm pN1;
Micrometastasis: >0.2 mm to </=2 mm pN1 mi;
ITC – individual tumour cells – microscopic clusters and single cells </= 0.2 mm pN0(i+).

Macroscopic handing of SLN is important. The lymph node and adherent fat must be examined. Lymph nodes up to 2 mm are embedded whole. Lymph nodes 2-4 mm in size are bisected and both halves submitted. Nodes that are 4 mm or more in largest dimension should be sliced at 2 mm intervals. Diagrammatic representation is available in the British Association of Gynaecological Pathologists document on protocols for processing of sentinel lymph nodes. (https://www.thebagp.org/download/bagp-sentinel-node-protocol/) A block index must be maintained.

Rationale of ultrastaging

When the initial H&E staining of the SLN does not identify metastatic disease, enhanced pathological assessment or ultrastaging should be performed. The incidence of false negatives when based on examination of a single H&E slide range from 5–58.3%. (45) False negative rates with conventional H&E were shown to be 58.3% in later a trial of sentinel node biopsy for vulval cancer, due to the additional detection of micrometastatic disease with ultrastaging. (46)

The recommended protocol involves cutting four sections at 200 μm intervals through the block and staining one section each with H&E and pancytokeratin stain (AE1/AE3 antibody). (47) One additional section is retained at each level in case there is a problem with H&E or IHC staining. This interval should ensure that a large percentage of micrometastases are identified.

4.3.3   Extranodal extension

Tumour extension outside the lymph node has been shown to be an independent predictor of poorer survival and is included in the FIGO and TNM staging systems. (35)

4.4   Ancillary studies

4.4.1   Ancillary studies in uVIN

The distinction between uVIN and dVIN is typically straightforward. However, the description of a basaloid variant of dVIN lacking maturation and potentially mimicking uVIN (48) or the co-existence of the changes of lichen simplex chronicus supervening on uVIN with increased apparent maturation (49) may create diagnostic difficulty. Immunohistochemistry for p16, a cyclin dependent kinase inhibitor that accumulates in transforming HPV infection, may help where diagnostic uncertainty arises.

4.4.2   Ancillary studies in dVIN

Diffuse strong p53 staining of the basal layer with suprabasilar extension has been described in ~85% of cases of dVIN. (50) Complete loss of staining (null pattern) has also been described. (51) In contrast, non-VIN epithelium shows wild-type staining, which is identified as staining of variable intensity in the cells. The different patterns may be difficult to interpret in small biopsy specimens where 'normal' epithelium is not available for assessment.

The utility of CK17 immunohistochemistry in the diagnosis of dVIN has been described, with strong, diffuse expression favouring dVIN over uVIN and lichen simplex chronicus. (52)

4.5   Pathology of Vulval Paget's disease and Invasive adenocarcinoma of the vulva

Vulval Paget's disease (VPD) is an uncommon, intra-epithelial adenocarcinoma, which arises most commonly on the vulva, usually in postmenopausal Caucasian women. Most lesions arise from a pluripotent epidermal stem cell within the interfollicular epidermis or folliculo-apocrine-sebacous units. Occasionally origin from an underling skin appendage adenocarcinoma or carcinoma of anorectal or urothelial origin is seen. In the majority of cases, disease is confined to the epithelium but in up to 20% of cases there is invasion into the underlying stroma. The risk of progression to invasive disease or metastasis following treatment for non-invasive VPD is low. (53)

The lesion is characterised by an apparently well demarcated, painful and erythematous eczematoid lesion, usually on the labia majora. Histologically, there is a population of large round cells with pale cytoplasm and nuclei with prominent nucleoli distributed throughout the epithelium as single cells or clusters. The tumour cells express cytokeratin 7, carcinoembryonic antigen and apocrine cell marker GCDFP15, which may help to distinguish VPD from other intra-epidermal neoplasms such as malignant melanoma *in situ*. The borders of the lesions seen clinically correlate poorly with the histological extent of the disease, which may account for the high rate of recurrence after primary surgery.

Data on the pathogenesis of VPD are, however, limited. Androgen receptors may be detected in >50% of VPD cases and represent a potential therapeutic target. Overexpression of HER2/neu (ERBB2) is present in at least one third of VPD lesions. HER2 positivity may confer a poorer prognosis with respect to invasion, recurrence and nodal metastasis but further study is needed to establish the precise biological significance of this marker. (54)

4.6 Pathology of vulval melanoma

Primary vulval melanoma is uncommon compared with those at ultraviolet light exposed sites (with a ratio of sun exposed skin to vulva melanoma of 71:1) and is typically diagnosed at older age. Up to 40% of women present with regional or distant metastasis. Compared with cutaneous and non-gynaecological mucosal melanomas, prognosis is relatively poor (5-year survival 58% for vulval melanoma compared with up to 81% for cutaneous disease). Lesions are typically asymmetric, with irregular borders and uneven pigmentation and there may be surface ulceration. Up to 25% may be amelanotic. Adverse prognostic factors are advanced clinical stage, Breslow thickness greater than 1 mm, vertical growth phase, ulceration and mitotic index over 1 per mm^2. Microsatellite lesions and perineural invasion are associated with increased local recurrence. (55, 56)

Understanding of molecular alterations within melanoma has led to expansion of treatment options and increased survival. Vulvo-vaginal melanoma appears to be different from both cutaneous melanoma and that from other mucosal origins. BRAF and cKIT mutations have been described. BRAF mutations were noted in 26% of vulvo-vaginal melanomas, lower than other sites. cKIT mutations have been found in 22% of vulvo-vaginal melanomas, compared with 8.8% in other mucosal melanomas. PD-L1 (56%) and PD1 (75%) were among the most frequent markers expressed, highlighting the potential use of immunotherapy targeted at this pathway. (57)

Pathological subtype	Precursor lesion(s)
Vulval squamous cell carcinoma (VSCC)	usual type vulval intraepithelial neoplasia (uVIN) (HPV-related); differentiated vulval intraepithelial neoplasia (dVIN) (vulval dermatoses-related)
Bartholin's gland carcinoma (squamous cell carcinoma (SCC), adenocarcinoma or transitional cell carcinoma)	uVIN for HPV-related SCC
Vulval malignant melanoma	Vulval acanthosis with altered differentiation (VAAD)
Invasive Paget's disease (adenocarcinoma)	Vulval Paget's disease (VPD) (adneocarcinoma in situ)
Basal cell carcinoma	

Table 4. Pathology of vulval malignancies and their precursor lesions

5 Treatment of primary disease

5.1 Surgery

5.1.1 Management of primary site

Vulval Squamous cell carcinoma (VSCC)

Surgery with curative intent is the mainstay of treatment for all locally limited vulval carcinomas. In FIGO stage IV tumours radical surgery is unlikely to be appropriate and surgery is limited to palliation of symptoms. For details of FIGO staging system please see Table 5. (58) For surgical treatment recommendations see Table 6 and Figure 2.

Modern management of vulval cancer is dictated by the size and site of the cancer and individualised to the patient. Historically, these tumours were managed by en-bloc radical excision of the entire vulva and the groin nodes, but evidence demonstrated no benefit for this technique over radical local excision, with separate incisions for the groin lymphadenectomy, which is far less mutilating to women and carries a far lower rate of morbidity and mortality (59, 60). The exception to this is in the presence of large and/or fixed nodes where recurrence in the skin bridge is higher and there may still be a role for en-bloc resection. (61)

Stage I	Tumour confined to the vulva
Stage Ia	Lesions ≤ 2 cm in size, confined to the vulva or perineum and with stromal invasion ≤ 1mm. 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

Table 5. International Federation of Gynecology and Obstetrics (FIGO 2014) staging system [35]

Treatment should be carefully planned pre-operatively, and ideally diagrams drawn for the patient to ensure adequate consent is achieved. Patients should be warned about the effects on sexual function following surgery, especially if the clitoral area is involved. Showing patients images of outcomes of surgery of previous patients can be useful to inform the consent process, as is commonly done in breast cancer.

The aim of surgery for the primary tumour is removal of the cancer with clearance at all margins, including the deep margin. Historically, a 1-2 cm macroscopic tumour-free margin was recommended on the basis of very limited retrospective data. More recent studies have shown that margins should be clear of disease, but that large negative margins are not required in node-negative patients treated with surgery alone (62-66) and a another contemporary series did not show an association with margin status unless margins were <2 mm. (67) A systematic review of prognostic factors in vulval cancer found a 4% annual local recurrence rate and that margins <8 mm were not associated with an increased risk. (68) Vulval recurrence is more often a new primary tumour within an area of field change as indicated by the presence of lichen sclerosus or VIN at the margins. (40, 69)

The planned excision margins should be marked out with a ruler and marker pen prior to commencing surgery. Care should be taken that this is in the natural state, i.e. the tissue is not stretched prior to marking. Consideration should also be given to Langer lines to achieve optimal healing and cosmesis.

In tumours which arise in a background of dVIN or Paget's disease, consideration should be given to excising the whole of the abnormal area, although with lesser radicality, if feasible. Recurrence rates if margins are involved with dVIN are high. (21) (70)

Stage Ia VSCC

Small tumours can be managed by excision, ensuring margins are achieved all around the primary tumour, as described above. For most tumours primary closure can be achieved, but for posterior lesions, or larger lateral lesions, consideration should be given to reconstructive surgery (described below) to allow the defect to be more easily closed, and vaginal function maintained. This is especially the case in women with re-occurrence of VSCC where there may be less tissue available for closure.

Stage Ib VSCC

The management of these is determined by the location of the tumour. If the tumour is lateral of the midline a radical wide local excision should be undertaken, which can subsequently be tailored for best approximation of the tissues and cosmesis. If the tumour is peri-clitoral, an anterior vulvectomy will need to be performed, or if the tumour is close to the midline, surgery will often involve the contralateral side of the vulva to ensure an adequate margin is achieved, and the defect can be closed easily. Patients should be counselled about the risk of losing clitoris/clitoral sensation and the impact on sexual function. Where the lesion is close to the urethra consideration should be given to removing the distal 1-2 cm of the urethra to achieve an adequate margin, which does not usually compromise urinary continence.

Lesions in the posterior part of the vulva are best managed with a posterior vulvectomy, with care being taken to ensure the anal sphincter is not compromised, and that an adequate margin can be achieved on the anal margin. These incisions are difficult to close with primary closure, so consideration of reconstructive techniques should be made and involvement of the rectal surgery and stoma team may also be required.

Large or multifocal tumours may necessitate a radical vulvectomy. The principles of such surgery are to remove the tumour with macroscopically-free margins, encompassing the clitoris, both sides of the vulva, and the perineum. The vagina is transected to achieve this, and care is taken to ensure the urethral and anal margins are taken without compromise to the sphincters. A plane from the mons pubis down to the perineum at the level of fascia lata is developed, and the involved skin removed.

Principles of reconstructions are considered in section 5.1.4 and may involve primary closure or more complex reconstructive techniques. (71) However, healing by secondary intent, as was used historically, can achieve good results and may be appropriate in patients unfit for more complex interventions.

Stage II VSCC

The principles of adequacy of surgical margins are maintained with these tumours, and excision of the distal urethra and vagina should be considered. In cases where the anus is involved concomitant chemoradiotherapy (CCRT) (or neoadjuvant chemoradiotherapy) may be considered to shrink the tumour, thus allowing adequate margins to be attained surgically without compromise of faecal continence (see sections 5.2.2 and 5.3.2 for further details). (72-77) However, for some women, surgical excision may require formation of a colostomy, either as a temporary measure to aid wound healing after reconstructive techniques, or following surgery to remove the anus and lower rectum.

Stage III VSCC

Management of the primary tumour is the same for these as for earlier stages, removal of the groin lymph nodes is described later. Recurrence in the skin bridge between the positive lymph node and the primary tumour is low. (59)

Stage IV VSCC

Surgery rarely has a role in advanced disease. Palliative procedures may be considered to ease discomfort, which is otherwise difficult to control. In cases of fistulation of the tumour to bowel or bladder, de-functioning stomas and/ or urinary diversions or nephrostomies can be considered.
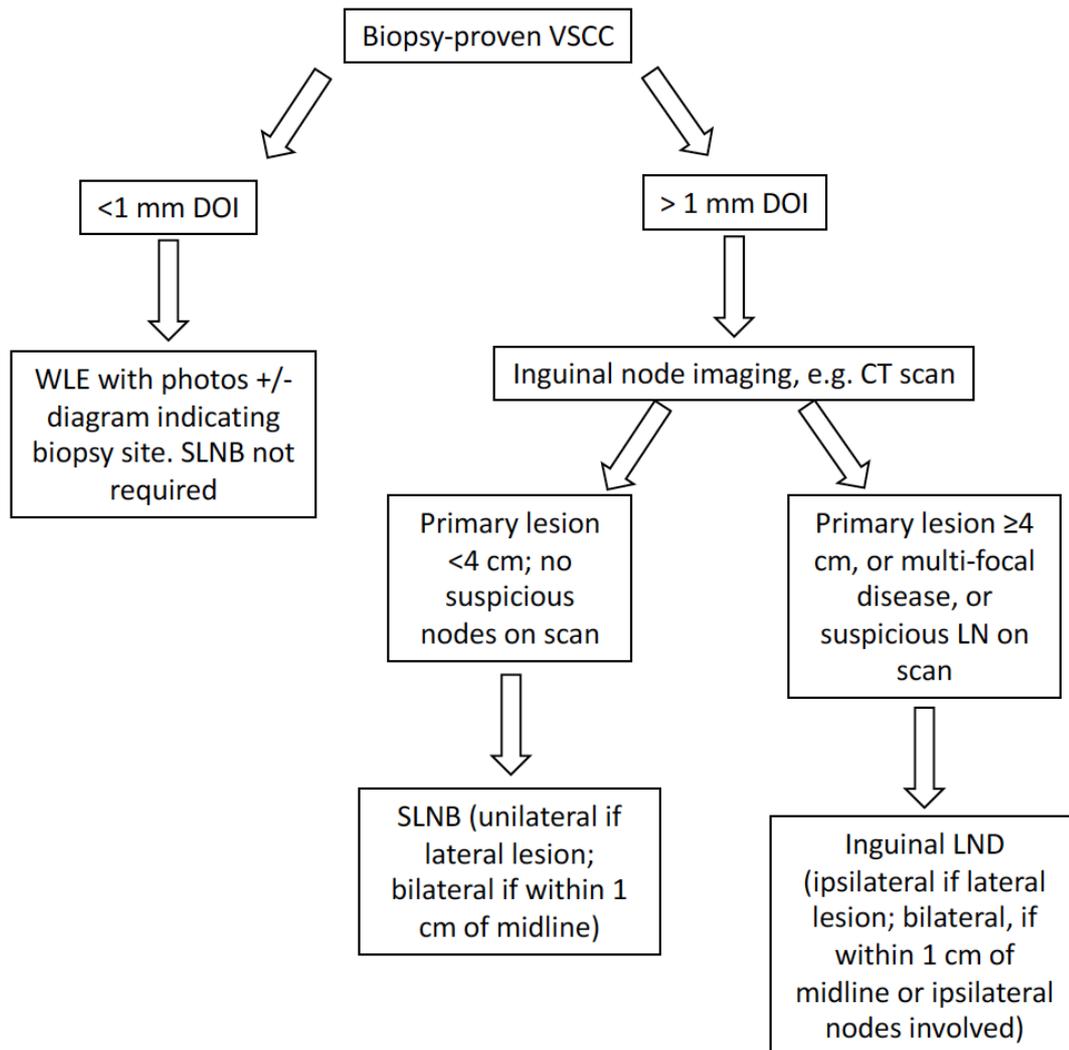
Figure 2. Management of primary lesion. VSCC = vulval squamous cell carcinoma; DOI = depth of invasion; WLE = wide local excision; CT = Computerised tomography scan; SLNB = sentinel lymph node biopsy; LND = lymph node dissection.

Recommendation	Grade of recommendation
Excision should be planned with macroscopic clearance of tumour by at least 1 cm *in situ* with the goal of achieving clear margins on pathological assessment. Closer margins may be considered to allow preservation of the clitoris, urethra or anus.	Grade D
As long as margins are microscopically clear of invasive disease, margins in the fixed specimen of >2 mm are acceptable. Data suggest that margins in the fixed specimen <2 mm are associated with higher rates of local recurrence. Surgeons should be aware that specimens shrink when fixed, so wider margins are required in situ to allow for this.	Grade D
If VSCC extends to the pathological excision margins, re-excision is the treatment of choice.	Grade D
Some patients require access to reconstructive techniques at the time of vulval surgery.	Grade D
Joint pre-operative planning with gynaecological oncology and reconstructive surgeons, including an examination under anaesthetic should be considered.	Grade D

Table 6. Recommendations for surgical treatment of primary site of VSCC

5.1.2   Surgical management of other vulval cancers

Non-squamous carcinoma can be classified in to four main categories:
- Bartholin's gland carcinoma (may be squamous, adenocarcinoma or transitional cell carcinoma);
- Adenocarcinomas arising from non-mammary Paget's disease;
- Basal cell carcinoma;
- Malignant melanoma.

For treatment recommendations of non-squamous cancer, see Table 7.

Carcinoma of the Bartholin's gland

These rare tumours make up approximately 5% of vulval malignancies. There are currently only 275 cases in the reported literature, (78) so evidence for management is based on case series or extrapolated from management of squamous cancers of the vulva.

These tumours arise from the Bartholin glands or their ducts, and classification is based on Honan's criteria. The tumour must be: in the correct position; deep in the labium majora; have normal overlying skin; and there should be some normal gland present. The glands and their ducts are comprised of several different cell types: the duct changes from stratified squamous epithelium at the vulval surface to transitional epithelium at the terminal ducts. There can therefore be a variety of histological types of Bartholin gland carcinomas including: adenocarcinoma; squamous carcinoma; and transitional cell carcinoma.

Because the tumours develop deep in the vulva, surgical management involves extensive dissection into the ischio-rectal fossa and potentially the anal sphincter. Surgery may require plastic

reconstruction. There is no current data regarding the use of sentinel node biopsy, hence inguinofemoral lymphadenectomy is recommended for the management of the groins.

Carcinoma of the Bartholin's gland is more commonly associated with metastatic disease at presentation with 60% presenting with stage III/IV disease in a recent case series. (79) Due to anatomical constrains, patients may require multiple treatment modalities or consideration of primary chemoradiotherapy. As with other VSCC, a staging CT should be undertaken before treatment planning (see section 3.5.4 for further details).

Treatment is based on previous experience of more common vulval carcinomas and case series, rather than randomized-control trial data. A review of 14 cases, from 1955-1980, recommended treatment by radical vulvectomy and inguinal-femoral lymphadenectomy, similar to other vulval carcinomas. (80) Another series of 36 patients was based on 30 years' clinical experience. (81) Nine patients had stage I disease, 14 stage II, ten stage III, and two stage IV. The five-year survival rate was 84%. Recommended treatment was wide local excision, with ipsilateral lymphadenectomy and where indicated, radiotherapy to the vulval and regional lymph nodes. Post-operative radiotherapy reduced the local recurrence rate from 27% to 7%. See section 5.2 for discussion of recommended adjuvant treatment options.

Basal cell carcinoma

Basal cell carcinomas (BCC) are rare (~5% of vulval cancers), normally behave in a locally invasive manner and only metastasise to lymph nodes if very large and invasive. (82) Local excision is recommended, with macroscopic clearance, and recurrence is associated with involved margins. Surgery should be performed with the aim to achieve margins free of microscopic disease (RO). In a retrospective series of 45 patients, the mean age of presentation was 76 years and most died of other causes. (82) Groin node surgery is not recommended unless there is clinical evidence of nodal disease.

For patients with multiple basal cell carcinomas (e.g. in Gorlin's syndrome) the surgical management should take in to account the symptoms and tumour burden and be managed in conjunction with dermatology and plastic surgery.

Vulval Paget's Disease

Vulval Paget's Disease (VPD) is a rare disease with only few case series presented in the literature. Invasive VPD represents 1-2% of all vulval cancer. However, the literature very poorly differentiates non-invasive VPD, invasive VPD, vulval adenocarcinoma and VPD with underlying malignancy, so the proportional incidence is difficult to estimate. VPD may be asymptomatic or present with itching, burning and irritation. VPD classically presents as an erythematous plaque with white scaling, called "cake-icing scaling". However, it can present with a variety of colours with nodules or plaque-like disease at presentation.

Patients with VPD may have an increased risk of an underlying malignancy and one study estimated a standardized incidence ratio of 1.39 (95% CI of 1.11–1.73. (83) The risks are lower than with Mammary Paget's Disease and somewhat uncertain due to lack of age standardisation in studies and whether an underlying invasive ano-genital adenocarcinoma is considered to be an associated malignancy, or not. However, underlying urological, colorectal, uterine and breast cancers have been reported. In one longitudinal study of 89 patients with VPD, 41 (46.1%) were diagnosed with 53 synchronous or metachronous cancers and seven (7.9%) had invasive vulvar cancer with ≥1 mm depth of invasion. (84) Cystoscopy, colonoscopy, hysteroscopy, CT and breast examination have therefore been

recommended at diagnosis. (85) However, more recent data from the Dutch pathology registry suggests that routine screening for secondary malignancies could be safely omitted. (86)

Treatment for VPD consists mainly of surgery +/- lymphadenectomy, if there is evidence of >1 mm depth of invasion. (87) The Cochrane review of treatment of Paget's disease in 2013 noted that there was an absence of evidence in treatment of VPD and that good quality studies were required; this situation has not changed. (87)   Recurrent disease is common (60-70%) and is as frequent in those with microscopically clear margins compared to those with involved margins. (88). Further excision may not reduce the risk of recurrence and alternatives, including imiquimod or watchful waiting, should be strongly considered, if invasion is excluded. There are no data regarding the safety or effectiveness of sentinel lymph node biopsy in VPD with evidence of invasion >1 mm and at present lymphadenectomy, whether ipsilateral or bilateral, depending on position, would be recommended.

A number of small non-randomised studies have looked at the effect of imiquimod on non-invasive VPD and demonstrate good response rates. These were summarised in a review article that concluded imiquimod seemed to be effective. (53) However, they also noted that treatment schedules differ greatly between the studies; duration of treatment ranged from 5 to 26 weeks and there is a significant risk of publication bias. In the studies included in their narrative review, 64 women with VPD were treated with imiquimod cream. Eight women were reported to have residual disease after treatment and 43 (67%) had a complete response, and a further 13 (21%) had a partial response. (53) Another systematic review of imiquimod in Paget's disease identified case reports and case series evidence from 63 patients. (89). They drew similar conclusions and noted that imiquimod may have a place in the treatment of VPD, especially in those with involved margins or to avoid surgery. The recurrence rate for those with a complete response (two of 35 women (5.7%)) was an order of magnitude lower than in studies of surgery, even with complete margins, although the follow up periods were short, recurrence rates not based on routine biopsy and numbers included small, so an RCT comparing surgery with imiquimod is urgently required and these data should be interpreted with caution.

Small case series have examined the use of radiotherapy and photodynamic therapy for treatment of VPD. Clinical responses have been reported and are summarised in a narrative review, however, the certainty of the evidence is very low and risk of reporting bias is very high. (53)

As with melanoma *in situ*, the risk of recurrence or development of invasive disease is high (~70% in one series (88)) and, with lack of data to guide recommendations, long-term follow up in a specialist pre-malignant vulval disease clinic is suggested. (90)

Malignant melanoma

Malignant melanoma is the second most common vulval malignancy after squamous cell carcinoma, representing 7-10% of all vulval cancers. Relapse rates are high and correlate with the depth of invasion (Breslow thickness). (91) An international study of vulval cancer, VULvar CANcer, involved 100 international centers. (92) Of the 1727 patients included, 42 were diagnosed with vulval melanoma (2.4%). During a mean follow up period of 44.1 months the recurrence rate was 50%. The mean overall survival for vulval melanomas was 45.9+/-4 months and the 5-year overall survival rate was 78.6%. Tumor size was the only significant prognostic factor for local recurrence (P = 0.003). Width of margins, lymphadenectomy rate, adjuvant treatment were not associated with recurrence or overall survival. Distant recurrence was related to The American Joint Committee on Cancer (AJCC) staging system, which includes prognostic factors important for cutaneous melanoma (including tumor thickness, tumor ulceration, status of regional lymph nodes, site of distant metastasis, and serum lactate dehydrogenase). Younger age was associated with an improved overall survival (P < 0.001). Vulval

melanoma treatment recommendations are covered by the recent Ano-uro-genital Mucosal Melanoma Full Guideline, which should be consulted for more detailed evidence and recommendations. (1)

All vulval melanoma should be discussed in both the gynaecology specialist MDT and the melanoma MDT. There should be appropriate pathways to enable effective communication between teams, particularly with regards to potential trial allocation.

Currently there is no evidence that survival of gynaecological melanoma has improved over the last 40 years. (93) However, novel immunotherapy agents are starting to show to improved survival in cutaneous melanomas and should be considered. Patients therefore should be tested at least for c-KIT and BRAF mutations, although rare in vulvo-vaginal melanomas. (20, 94)

Inguino-femoral lymphadenectomy has not been shown to improve survival. Sentinel lymph node detection has been used in vulval melanoma and may influence treatment choices. Recent NICE guidance suggests a role for immunotherapy (Nivolumab) in improving recurrence-free survival for patients with node-positive surgically resected melanoma. (95) Surgical resection of involved regional nodes may be considered for palliation and improve quality of life, although groin node surgery is not without significant morbidity. (96)

Surgical management should consist of a wide local excision to achieve margins free of microscopic disease by >1 mm (R0) in the least radical fashion. There is no evidence that more radical surgery is beneficial. (92) If margins are microscopically involved (R1), further salvage surgery is normally recommended. If this is not possible, or is declined, options involve:

- Watch and wait, treating recurrences as identified and appropriate at the time;
- Adjuvant radiotherapy with the aim of reducing local recurrence;
- Systemic therapy.

All patients should be encouraged to participate in clinical trials, as appropriate.

Recommendation	Grade of recommendation
Bartholin's Carcinoma	
Patients with Bartholin's gland carcinoma may need multi-modal treatment and full body imaging with CT CAP is recommended prior to surgery, as disease is more likely to present at an advanced stage. (Grade D)	Grade D
Vulval Paget's Disease	
Consider investigations to exclude a co-existing malignancy of the breast, gynaecological, urological and colorectal tracts at diagnosis.	Grade D
Surgery should aim to remove invasive visible disease with macroscopically clear margins. Microscopic involvement of the margins is common and re-excision may not be of benefit.	Grade C
Imiquimod may be of benefit and reduce the need for surgery, if invasive disease is excluded.	Grade C

Recommendation	Grade of recommendation
Radiotherapy or photodynamic therapy have been used in VPD, but the certainty of this evidence is very low and should be considered with caution.	Grade C
Vulval Malignant Melanoma	
Patients should be treated with close collaboration of the gynae-oncology and melanoma MDTs.	Grade D
Surgery should aim to achieve an R0 resection (no microscopic disease within <1 mm of margins) with the least radicality.	Grade C
Sentinel node dissection may help to guide adjuvant immunotherapy and should be considered after discussion with the Melanoma MDT.	Grade D
Metastatic regional nodal disease may be considered for removal as treatment may improve quality of life, but without evidence of survival benefit.	Grade D
Patients should be treated with close collaboration of the gynae-oncology and melanoma MDTs.	Grade D

Table 7. Recommendations for treatment of rare vulval malignancies

5.1.3   Management of inguinal lymph nodes

Background

For recommendations for management of inguinal and pelvic nodes, see Table 8. In keeping with squamous cell carcinomas at other sites, the presence of lymph node metastases in VSCC is of crucial prognostic importance. (97, 98) The FIGO staging was updated in 2009 to reflect the impact of size and number of lymph node metastasis on outcome. (58) Imaging modalities including ultrasound, MRI and CT/PET- CT have been advocated for pre-operative staging, but both sensitivities and specificities for these techniques remain suboptimal. (58, 99) In the light the poor survival associated with groin node recurrence, surgery has retained its central role in the detection of lymph node metastasis. Anatomical studies have demonstrated reproducible lymphatic drainage with lymphatic flow from posterior to anterior. The lymphatics do not cross the labio-crural folds but decussate in the mons pubis. (100) Tumour spread in the lymphatics is embolic in early stage disease, with 'midline' tumours having the potential to drain to both groin fields. The consistently low rate (<1%) risk of lymph node metastasis for tumours of ≤1 mm depth of invasion (101) means that for this limited group, surgical assessment of the inguinal nodes can safely be omitted. Lymph node dissection should also be omitted for basal cell and verrucous subtypes. For recommendations on lymph node management and initial management flowchart see Table 8, Table 9, Table 10 and Figure 2.

Formal Inguinofemoral lymphadenectomy is associated with high-rates of complications, including wound breakdown and lymphoedema. (46) Sentinel node dissection (SLND) should be standard of care, where indicated, as it is both accurate and associated with reduced morbidity. (46, 102) Sentinel node(s) can be identified with vital or fluorescent dyes and radioisotopes. The use of combinations of radiocolloid and vital (blue) dye is associated with high detection rates and low groin recurrence rates (<3%) when used in large studies and cases of unifocal, small (T2, <4 cm) primary tumours. (46, 103, 104) False negative rates were around 9% in a meta-analysis which included multiple smaller studies. (104) The technique is associated with reduced sensitivity and higher false negative rates for larger tumours. (105) Formal lymphadenectomy should therefore be standard for larger tumours (T3, >4 cm).

Fluorescent detection with indocyanine green fluorescence (ICG) may outperform blue dye, but performance data for SLND using fluorescence alone are lacking and body habitus may limit the utility of this approach. (106, 107) The combination with radioisotope and ICG may have advantages when compared to the combination of radioisotope and blue dye. (107) The use of vital dye alone is not recommended due to low detection rates (72). Case selection and appropriate training are of paramount importance. Recommended criteria for the use of SLND in early vulval cancer are listed in Table 9. The European Society of Gynaecological Oncology (ESGO) guidelines (44) recommend a minimum throughput to maintain competency in this technique. The exact number of cases required is a subject of debate. A centralised database of procedures could help with quality control on a national basis.

Preoperative lymphoscintigraphy is currently employed by most centres and is advised to enable the preoperative identification of the number and location of sentinel nodes. For tumours that are truly midline (within 1 cm of midline), bilateral drainage should occur. Where only unilateral drainage is identified for midline tumours, inguinofemoral lymphadenectomy should be performed for the groin in which the technique has failed.

Recommendation	Grade of recommendation
Treatment to the groin(s) is required where the depth of the primary tumour is >1 mm (>FIGO 1a; pT1a)	Grade C
Sentinel node dissection is the treatment of choice for small (<4 cm), unifocal tumours without clinical or radiological evidence of lymph node metastasis at presentation providing representative injection is possible and the tumour does not encroach on the urethra, vagina or anus	Grade B
For tumours >4 cm and/or multifocal disease, inguinofemoral lymphadenectomy via separate groin incisions is recommended	Grade C
For tumours >4 cm and/or multifocal disease, inguinofemoral lymphadenectomy via separate groin incisions is recommended	Grade C
Lymphadenectomy should include removal of the deep femoral nodes	Grade D
Preservation of the saphenous vein may reduce the risk of post-operative complications and is recommended where feasible	Grade D
Patients with advanced or recurrent disease require individualised, multimodal management and the optimal choice and order of treatment modalities should be decided within the multidisciplinary team	Expert opinion (✓)
The removal of bulky (>2 cm) pelvic nodes should be considered due to the limitations of radiotherapy in controlling bulky nodal disease	Expert opinion (✓)

Table 8. Recommendations for management of groin nodes

Pathological assessment of the SLN

Intraoperative evaluation and/or frozen sectioning of the SLN can be performed in an attempt to prevent a second surgical procedure. However, this approach has an increased risk of missing micrometastases on final pathology from the loss of tissue arising from processing for frozen- section assessment. (104, 108). Current evidence would suggest that nodes negative on standard processing with H&E staining should be subject to ultrastaging, with serial sectioning (at 200 µm) and immunohistochemistry with epithelial marker (usually AE1/AE3) to detect macro- and especially micro-metastatic disease.

Metastatic disease found by ultrastaging in patients who are node negative by conventional histology is associated with higher recurrence rates. (109) The use of combination detection techniques with pathological ultrastaging is both highly active and cost effective in the management of early stage disease. (104, 108). The pathological protocol for assessment of the sentinel lymph node is discussed in detail in section 4.3.2.

Management of the positive SLN

Where disease is identified in the SLN, additional treatment to the groins should occur as there is a significant risk of disease (8-35%) in other nodes within the lymphatic basin. (43, 46) At present, treatment with ipsilateral inguinofemoral lymphadenectomy at least is recommended. For tumours with bilateral drainage and unilateral positive SLN(s), the majority of centres opt for bilateral inguinofemoral lymphadenectomy. This approach is largely based on historical data and may not consider the additional information provided by sentinel node dissection. A recent study suggests that inguinofemoral lymphadenectomy could safely be limited to the groin with the positive SLN(s), potentially sparing the patient from the morbidity associated with formal lymphadenectomy in the SLN negative groin. (110) The safety and efficacy of omitting lymphadenectomy in SLN positive patients in favour of radiotherapy alone was the subject of a recently completed prospective study (GROINSS-VII, Cancer Research UK trial number CRUK/08/019), which should report in the near future. (32) However, the trial protocol was changed, after interim safety analysis, to mandate groin node lymphadenectomy in the presence of more than microscopic groin node involvement (>2 mm), due to a higher than expected recurrence rate in the arm that received radiotherapy alone. It should be noted that the finding of ITC in the SLN is not regarded as representing metastatic disease for the purpose of subsequent management decisions.

Follow up after SLND

The optimal follow-up protocol for detecting groin recurrence in cases of negative SLND is yet to be established. Salvage treatment with inguinofemoral lymphadenectomy and radiotherapy may be effective in cases of lymph node recurrence following false negative results at sentinel node dissection. (111) Recurrence risk is greatest in the first two years (111, 112) and follow-up regimes should be aimed at detecting metastases at an early stage during this period. Ultrasound is more effective at detecting lymph node metastasis, but data to support the cost-effectiveness of routine ultrasound in these patients is limited. (113)

Criteria	Comment
Unifocal disease	False negative rate higher for multifocal disease
Depth of invasion >1 mm	Low risk LN metastasis if ≤1 mm
Tumour <4 cm in vivo	>4 cm associated with higher false negative rate
Representative peri-lesional injection is possible	Risk of false negative if non-representative injection
Tumour should not encroach on urethra, anus or vagina	Representative injection not possible
No clinical or radiological evidence of involved nodes	Cross sectional imaging recommended

Table 9. Criteria for SLND

Recommendation	Grade of recommendation
Sentinel node dissection is the procedure of choice for small (<4 cm), unifocal tumours without clinical or radiological evidence of lymph node metastasis at presentation providing representative injection is possible and the tumour does not encroach on the urethra, vagina or anus	Grade B
There is a clear learning curve for SLND and the technique should be performed by clinicians/centres with appropriate levels of training and expertise to maintain practice	Expert opinion (✓)
The use of radioisotope is mandatory for SLND. Vital or fluorescent dyes may be used in addition to radioactive tracer	Grade B
Preoperative lymphoscintigraphy is recommended to enable the identification, location and number of sentinel nodes.	Grade C
When a sentinel lymph node (SLN) is not found (method failure) inguinofemoral lymphadenectomy should be performed. (✓)	Expert opinion (✓)
For tumours involving the midline, bilateral SLND should be performed. The identification of a unilateral SLN in such tumours should be regarded as 'method failure' and inguinofemoral lymphadenectomy of the contralateral groin (no sentinel found) is recommended. (✓)	Expert opinion (✓)
Intra operative assessment of the SLN by frozen section can potentially be used to avoid the need for a second procedure in node positive disease. However, caution is required due to the loss of tissue that arises from this process and the potential risk of a false negative sentinel node. (	Grade C
Pathological assessment of the SLN should include ultrastaging when the node is negative on standard H&E sectioning. Ultrastaging should include serial step sectioning at least every 200 µm with the use of immunohistochemistry where the H&E sections are negative.	Grade C
When metastatic disease is identified in the SLN, inguinofemoral lymphadenectomy for the groin affected by metastatic disease is the current treatment of choice.	Grade C
Evidence does not suggest that sentinel nodes with isolated tumour cells should be treated as positive nodes.	Grade C

Table 10. Recommendations for sentinel lymph node dissection

Groin node dissection

Inguinofemoral lymphadenectomy remains the primary treatment modality for the groins in tumours of >4 cm. Lymphadenectomy should include the medial, deep femoral nodes as omission of this group is associated with a higher risk of groin node recurrence. (114) There are conflicting data to support the preservation of the great saphenous vein to reduce the risk of subsequent complications, particularly lymphoedema, since in some studies differences did not reach statistical significance. However, since in many other series there was a statistically significant increased morbidity in the patients where the saphenous vein was not preserved, we would advise to preserve the saphenous vein when and where possible. (115, 116) There is no consistent evidence as to the impact of node count on prognosis in

vulval cancer. (117-120) In early disease, spread in the lymphatics appears to be embolic and separate incisions can be used for the vulval and inguinal dissections to reduce surgical morbidity. (59, 121) For lateralized tumours >1 cm from midline, bilateral lymphadenectomy can be omitted in favour of ipsilateral lymphadenectomy, although for larger tumours the risk of contralateral involvement rises. (122) Contralateral inguinofemoral lymphadenectomy should be performed when ipsilateral nodes show metastatic disease. (68) For patients with positive nodes, the number and size of lymph node metastases determines outcome. (43, 123-125) Extracapsular spread of tumour is associated with particularly poor prognosis. (123, 124)

The optimal management of clinically enlarged, metastatic pelvic lymph nodes remains to be defined, but treatment is typically by combination of surgery and radiation. Debulking of bulky (>2 cm) nodes is recommended prior to adjuvant radiotherapy, as radiotherapy alone may fail to sterilize bulky nodal disease. (44) In an effort to reduce complications from dual modality treatment, lymph node debulking rather than formal lymphadenectomy may be used prior to (chemo)radiotherapy. (126, 127) Where inguinofemoral lymph node metastases are identified at lymphadenectomy, adjuvant treatment with radiation is associated with improved survival for cases with > 1 metastatic lymph node and/or the presence of extracapsular lymph node involvement. (128) Where imaging suggests negative pelvic nodes, adjuvant radiotherapy should include at least the ipsilateral groin and the distal part of the iliac nodes with an upper limit at the level of the bifurcation of the common iliac artery. (44) Treatment to the ipsilateral pelvic nodes should be considered due to the high risk of pelvic node involvement in this group. Treatment with chemoradiation appears superior to pelvic node dissection. (129)

Complications of lymphadenectomy

The high incidence of complications (particularly wound breakdown (34%), lymphocyst formation and lymphoedema (25-45%)) following inguinofemoral lymphadenectomy has been confirmed in recent studies. (46, 130) A variety of strategies have been suggested in an effort to reduce the rate of complications, but high-quality evidence to support recommendations is lacking. Preservation of the great saphenous vein during lymphadenectomy may reduce the risk of cellulitis and lymphoedema and is recommended. (116) Suction drainage is usually employed after lymphadenectomy, but the optimum management of wound drainage is yet to be defined. (131, 132) The use of fibrin sealant does not reduce lymphoedema and may increase post-operative infection rates. (133) Transposition of the sartorius muscle has been advocated, particularly where adjuvant groin radiation is anticipated, but more recent data have suggested that the technique is not associated with any benefit in wound complication or lymphoedema rates. (134) See section 7.2 for management of lymphoedema.

Recurrent disease after lymphadenectomy

The outcome following inguinal recurrence after lymphadenectomy is historically regarded as poor. (135) Limited recent data suggests that long-term survival can be achieved with multimodality treatment (OS 50% at 7 years; n=30). (112) Restaging with CT is advised and combination treatment with surgery and post-operative chemoradiation (in radiotherapy naïve patients) is typically employed. Individualised treatment in a multidisciplinary setting is essential for these complex patients.

5.1.4   Reconstructive surgery

Since the publication of first RCOG guidelines for the management of vulval cancer in 2006, there has been a 'gradual increase in the number of women having … reconstructive or plastic surgery input'. (90) The European Society of Gynaecological Oncology Vulvar cancer guidelines also advise 'availability of reconstructive skills for both early & late disease'. (44) However, despite increasing use of reconstructive techniques in gynaecological oncology surgery, there is very limited evidence in this field, both regarding when reconstructive surgery is needed, and which techniques to use. This section is therefore based on personal experience, case reports & series, & extrapolations from other

reconstructive surgery fields. The vast majority of women will have good results following primary closure with appropriate release techniques. Leaving wounds open to heal by secondary intention is also a valid option in some cases and can achieve good functional and cosmetic results.

Aims of reconstructive surgery

In the setting of vulval cancer, the primary aim of reconstructive surgery is to facilitate complete, curative surgical resection of the disease with appropriate margins and preservation of organ functions. Secondary aims are to enable wound healing by primary intention and to reduce morbidity due to scarring.

The anatomy of the vulva means that for small resections, direct closure is often possible. However, wider resections or repeated small excisions can lead to tightness & scarring around the vaginal introitus with dyspareunia, pain on passing urine or even discomfort on sitting and walking. Ultimately, tension of wound closure will reduce blood supply to the skin margins and therefore affect wound healing. Radiotherapy reduces effective cell division and therefore reduces the skin's ability to heal. Irradiated wounds may be particularly slow to heal, if closed under tension. Reconstructive surgery techniques can be used to reduce tension on previously irradiated skin, or to introduce non-irradiated tissue into the wound bed.

The reconstructive surgeon will employ a variety of techniques to close a perineal wound, taking into account the disease pathology and tissues to be excised; local anatomy; comorbidities; and patient preferences. These techniques include split and full thickness skin grafts; local & regional flaps; and free flaps. Similar techniques can also be used to release areas of tight, uncomfortable scar after excision & direct closure. The option of primary closure using release techniques is appropriate for the very large majority of resections and consideration should be given to leaving wounds open to heal by secondary intention in selected cases.

Surgical planning

1. The resecting surgeon should not be tempted to limit their surgical excision by the constraints of soft tissue closure.

2. Before surgery, there will ideally be a combined excision/reconstruction examination, either in clinic or under anaesthesia, to plan which tissues to excise and allow full pre-operative counselling regarding reconstruction.

3. If the anal margin is involved by the disease, the two potential approaches are: temporary or permanent stoma with excision of the required amount of anal margin; or neo-adjuvant (chemo)radiotherapy with the aim of down-sizing the disease & allowing preservation of the anus.

4. If the resection margin will lie within 1 cm of the anal margin, consider faecal diversion, either as a combined procedure or 2 weeks pre-operatively. Usually, margins greater than 1 cm do not require a stoma.

5. Local flap reconstruction is possible after radiotherapy to the flap field, but the length to breadth ratio of the flap may need to be modified to avoid tip necrosis.

6. Skin grafting is also possible after radiotherapy, though graft 'take' may be reduced if the wound bed has a poor vascular supply. Local flaps may be quicker to heal than skin grafts in the post-radiotherapy wound bed

7. If excision margins are difficult to assess, frozen section should be considered before planning flaps for reconstruction.

8. After flap reconstruction, if lateral margins are incomplete then the margin of the flap & an appropriate amount of native tissue can be excised. If the deep margin is involved, a thick flap may be lifted in a more superficial plane and replaced after excision of deeper tissues. However, a thin flap may need to be entirely excised with the underlying soft tissue to obtain a clear margin. For this reason, if there is uncertainty about surgical margins, delayed flap reconstruction with either dressings, direct closure or skin graft while pathology is obtained should be considered.

The complex three-dimensional anatomy and specialized skin of the different regions of the vulva make for a reconstructive challenge. It is difficult to completely match excised vulval skin in terms of colour, texture, hair, secretions and thickness. However, the vulval region has a rich blood supply so local and regional flap options abound. See Table 11 for a summary.

1. Skin grafts: split or full thickness skin grafts are useful for skinning vulvectomies where a local flap would be more bulky than the tissue removed. Split skin grafts are more prone to contracture than full thickness grafts. Full thickness graft donor sites are directly closed so a donor site with adequate laxity is needed.
2. Dermal replacement: this is a developing field, and may be of use in the future as an adjunct to split skin grafting to allow for more pliable skin.
3. Local flaps: rhomboid flaps, lotus petal flaps and local advancement flaps can be used unilaterally or bilaterally even in the face of prior surgery or radiotherapy. Consider the impact of the donor site scar; thickness of the flap (they may require secondary thinning); and potential for lymphoedema after lymph node dissection which may affect wound healing.
4. Distant flaps: gracilis, rectus abdominis and anterolateral thigh flaps will reach the vulval wound without tension and offer more versatility for larger or deeper defects, for example after exenteration. They may be useful if previous surgery, radiotherapy or lymphoedema have compromised local flap options.
5. Free flaps: these are rarely used in the vulva because of the diverse local options, but offer the possibility of a more tailored reconstruction.

5.1.5 Vacuum-assisted Closure (VAC)

Vacuum-assisted closure or VAC dressings, are infrequently useful in management of vulval wounds, due to the challenges of obtaining an adequate seal due to local anatomy. VAC dressing may have a limited place in management of inguinal wounds that have opened up due to infection; a Cochrane review suggest that negative pressure dressings may decrease the time of wound healing of wounds by secondary intent, but data are limited and of very low certainty. (136) Data from another Cochrane review of negative pressure dressings following primary closure, suggest that there may be a slight decrease in surgical site infections, but again the certainty of evidence is very low. (137)

Graft and flaps	Pros	Cons
Split skin graft	Don't add bulk from underlying tissues, unlike flaps	Prone to contracture; effect on donor site
Dermal replacement	Used with split skin grafts to allow more pliable skin	Still in development
Local flaps: rhomboid; lotus petal; local advancement	Unilateral or bilateral; relatively simple	May be thicker than needed, requiring secondary thinning; affected by previous radiotherapy; risk of lymphoedema affecting wound healing
Distant flaps: gracilis; rectus abdominum;	Minimal tension; option to cover large and deeper defects; can be	Bigger/thicker flap may cause issues

anterolateral thisgh flap	taken from skin outside of previous radiotherapy/lymphoedema area	
Free flaps	More tailored reconstruction	Higher risk of devascularisation

Table 11: Reconstructive options for wound closure

5.2 Radiotherapy

Surgery is commonly the treatment of choice for vulval cancer, but there may be indications for radiotherapy, with or without concomitant chemotherapy, in both the primary and adjuvant setting. See Table 12 for recommendations for adjuvant/neoadjuvant treatment.

Primary radiation therapy may need to be considered in patients deemed inoperable due to extent of tumour (or where there is sphincter-threatening disease and patient wishes to avoid a stoma), and/or fitness for anaesthesia. In this scenario, the intent of treatment may be radical or palliative depending on the specific circumstances.

Adjuvant radiation is utilised in patients with high-risk disease where there are two or more positive inguinal lymph nodes or a solitary node with extra-capsular spread. Radiotherapy may also be considered in the post-operative setting, if the resection margins are positive and further surgical excision is not possible. (138) Significant damage/ impairment of structures, such as anus, urethra, and clitoris should be considered when planning surgical re-excision and balanced against the risks of radiotherapy. (44) In case of close, but clear, pathological margins, post-operative vulval radiotherapy may be considered, to reduce the frequency of local recurrences, but data are limited with no overall survival benefit. (139) There is no consensus for the threshold of pathological margin distance below which adjuvant radiotherapy should be advised, although margins of <2 mm are associated with increased local recurrence rates. (44, 67)

Radiation is typically delivered via external beam, ideally within 6 weeks of surgery. (44) However, in selected patients a boost may be applied with an interstitial implant. Occasionally, an implant may comprise the sole treatment for a small localised recurrence, but in the majority of recurrences external beam, alone or in combination with chemotherapy, would be the standard approach. This will be discussed in more detail in section 6.

5.2.1 Adjuvant radiation / chemoradiation therapy

Probably the most frequent indication for external beam radiotherapy will be for patients who have undergone surgical resection and in whom the histological examination has demonstrated positive lymph nodes. Most of the experience has come from trials conducted by the Gynaecological Oncology Group (GOG) who performed a number of studies in the 1980s and 1990s. These showed that adjuvant radiation therapy to the groins bilaterally was of benefit, if there were two or more lymph nodes involved, or if there were one or more nodes with extracapsular spread. (129)

Techniques for both surgery and radiation have changed considerably in the past 10-15 years. The introduction of Intensity Modulated Radiation Therapy (IMRT) and Volumetric Modulated Arc Therapy (VMAT) have changed radiation therapy practice considerably. This advanced technology has developed in parallel with the greater use of contrast enhanced CT or MRI imaging to optimise radiotherapy planning which not only allows the target volume to be delineated more precisely but also allows identification of the Organs At Risk (OARs). This greater precision has helped to reduce short-term toxicity and hopefully long-term as well. Patients are planned with a contrast CT scan to identify the vessels, which allows the clinical oncologist to delineate the site of lymph nodes. In addition, the OARs such as bladder, rectum and small bowel are highlighted to enable the planning physicist to

minimise the dose to these structures. (140, 141) This leads to the potential double benefit of theoretically reducing late toxicity while simultaneously facilitating dose escalation, which may improve the chances of local control and overall survival. Traditionally doses of at least 4,500 and up to 5,000 cGy in 25 fractions were delivered to the inguinal and pelvic nodes, (but escalation to 5,500 or even 6,000 cGy may be considered with integrated boost). One retrospective review of 300 women with Stage I-IVA VSCC, treated between 1988 and 2009, showed that when doses of at least 5,600 cGy were used, recurrence rates were lower in those with close or positive margins. (142)

Modern interstitial techniques, using high-dose rate therapy, can use multiplane channels and allow coverage of the vulval resection margins. Additional care may be required in patients who have had skin grafts and close liaison with the gynaecological surgeon and plastic surgeon is recommended to ensure that this is carried out at the optimal time. One major challenge regarding interstitial implant therapy is that there is a diminishing pool of skilled clinical oncologists who are able to perform this procedure and consideration should be given to developing a number of supra-regional sites where this can be carried out. (74)

As stated in the current ESGO vulva cancer guidelines, the principle of chemoradiotherapy in vulva cancer is mainly based on evidence from other squamous cell cancers such as cervical, head & neck, and anal cancer, with the intent of sensitising the tumour to radiation. (44) On the basis of that, concomitant chemotherapy with radiation should be considered even in the absence randomised trial data specific to the vulva. Large population data analysis reported an increase in the use of adjuvant chemotherapy in addition to adjuvant radiotherapy in vulval cancer over time. (143) After adjustment for patient factors, adjuvant chemotherapy reduced the risk of death by 38% (HR 0.62, 95% CI 0.48–0.79, P= 0.001).

5.2.2   Primary site irradiation-primary treatment

While it is accepted that primary surgery is the preferred treatment, there will be cases where patients have unresectable disease, either because anterior and/or posterior exenteration is required with stoma formation, which the patient may not accept, or because patients are unfit for major surgery/anaesthesia. In these women, radical chemoradiotherapy should be considered. (144) Other options also include the use of neoadjuvant chemotherapy in an attempt to downsize the tumour and may avoid the need for exenterative surgery, although this is in the absence of RCT level data.

Treatment should be planned with contrast enhanced CT, the target volume consisting of the tumour at the primary site and associated bilateral nodal basins (inguinal and pelvic). Bolus may be required in order to maximise the dose to involved skin/subcutaneous tissue. Doses of at least 6,000 cGy will be required and this will typically be delivered over two phases: part one administering 4500 – 5,000 cGy to the pelvis/groins; followed by an additional 1,500 – 2,000 cGy photon or electron boost to gross disease. However, in selected patients, external beam radiotherapy can be followed by an interstitial implant to the residual disease in the vulva. The use of IMRT can also allow selective dose boosting to be carried out. (145)

The use of the interstitial implant to boost the dose is a useful option in centres that have the facilities and expertise to carry this out. Doses of the order of 4,500-5,000 cGy may be delivered to the primary site and an interstitial boost is given usually after a three to four-week gap to permit the acute radiation reaction to settle. There is no firm evidence to select the boost dose, but historically low-dose rate brachytherapy would give doses of around 2,500-3,000 cGy boost. When using high-dose rate, doses are adjusted to around 1,500-1,800 cGy in three fractions, dependent upon the external beam radiotherapy dose.

Concomitant cisplatin should be considered in fit patients receiving radical radiation therapy as the primary treatment using doses of 40 mg/m² weekly. (144) Regimens consisting of non-platinum drugs including mitomycin-c and 5-fluorouracil/capecitabine have also been described. An ongoing phase II single- arm study (NCT01595061) of the GOG- group is exploring the effect of concomitant cisplatin and gemcitabine with Intensity-Modulated Radiation Therapy (IMRT) in 52 patients with locally advanced SCC of the vulva. (146)

5.2.3   Palliative radiotherapy

A number of patients with surgically treated disease will develop a recurrence and, whilst there may be opportunities for salvage radiotherapy, in some situations the patient may not be suitable for radical treatment. These patients may have pain, bleeding, ulceration and local invasion into bladder and/or or rectum. Palliative radiation may alleviate distressing symptoms, but should be given as relatively short courses. The most frequent schedules will be 2,000 cGy in 5 fractions or 3,000 cGy in 10 fractions delivered over one or two weeks. In very frail patients who have active bleeding, a single fraction of 800 cGy or 1,000 cGy may be considered and this can be repeated if required. Palliative radiotherapy may also need to be considered at first presentation, where other treatment options are not accepted and/or clinically appropriate.

5.3 Chemotherapy

See Table 12 for recommendations for adjuvant/neoadjuvant treatment.

5.3.1   Squamous Cell Carcinoma

Chemotherapy has been used in the management of vulval cancer at multiple points: in a neoadjuvant setting to reduce the extent of surgery; and in the adjuvant setting with concomitant radiation, for node positive disease. Chemotherapy treatment for recurrent and metastatic disease is discussed in Section 6. The potential for using more targeted systemic therapies e.g. growth factor receptor inhibitors, biological agents and immunotherapy is also explored here.

5.3.2   Neoadjuvant chemotherapy for invasive squamous cell carcinoma

Systemic neoadjuvant therapy is reserved for vulval cancer patients who are either too unwell to undergo radical curative surgery/radiation, or for those whose large volume primary / nodal disease could be treated with more conservative surgery / radiation, if adequately down-staged. Publications in this setting are limited to small case series. Reports of response rates between 56-67% to various cytotoxic combinations in this setting date back to 1990 and include agents such as bleomycin, vincristine, mitomycin C, methotrexate, lomustine, 5-flourouracil, paclitaxel, carboplatin and cisplatin. (77, 147) Reported long-term survival was limited – e.g. 24% still alive at 3 years. (73) More recently infusional 5-FU with cisplatin has been evaluated as NACT for patients with locally advanced vulval cancer in small studies, with responses ranging from 20-100%. (75, 76) A very small study of seven patients -and two with recurrent metastatic disease- were treated with weekly paclitaxel (60 mg/m^2) and carboplatin (AUC 2.7), however, the study failed to show any response. (148) Another recent publication describes the use of platinum-based NACT or bleomycin alone in 32 and five patients, respectively. (72) Responses were documented in 30 patients (81%) and 27 proceeded to radical vulvectomy. Eleven women (40%) had residual tumour in groin nodes and underwent post-operative chemoradiation. At 49 months follow up 24/27 (88%) of the surgical patients had no evidence of recurrence. Conversely, Raspagliesi et al described the treatment of ten patients with cisplatin / paclitaxel +/- ifosfamide. (149) Nine patients subsequently underwent radical local excision or radical partial vulvectomy and bilateral inguino-femoral lymphadenectomy. The clinical response rate of all enrolled patients was 80%, whereas the pathological responses included one case with complete remission, two with persistent carcinoma in situ, and six invasive cancer cases with tumour shrinkage

of more than 50%. The authors concluded that based on the high response rates and manageable toxicity, NACT with paclitaxel and cisplatin with or without ifosfamide followed by surgery could be considered as a therapeutic option for locally advanced vulvar cancer. (75, 149, 150)

In analogy to the standard carboplatin and paclitaxel regimen given in other gynaecological cancer, the group by Amant et al, reported their experience with 3-weekly paclitaxel-carboplatin chemotherapy for patients with locally advanced vulvar cancer demonstrating clinical responses that enabled patients to have subsequent surgery. (151) The authors recommended that a prospective multicentre study should be performed in a larger series of patients in order to compare neoadjuvant paclitaxel-carboplatin with chemoradiation, based on these preliminary results.

A recent pooled analysis of published evidence addressing treatment of advanced vulval cancer by neoadjuvant or definitive chemotherapy (CT) or chemoradiation (CRT) analysed the factors influencing patients' survival. (152) A total of 97 patients with stage III and IV disease were included and re-evaluated, although results should be interpreted with extreme caution, as they are likely subject to significant selection bias. The pooled reanalysis found that neoadjuvant therapy plus surgery led to significantly better 5-year overall survival (73%) than definitive CRT (43%) alone. However, no significant difference was found between CRT (5-year overall survival 69%) and CT (77%, p=0.11) in the neoadjuvant setting. In addition, patients showing a positive response to CT or CRT had a better 5-year overall survival (67% vs. 20%, p=0.001). The authors concluded that NAC plus surgery can potentially improve survival of patients with advanced vulvar cancer.

A Cochrane review (153) evaluating the effectiveness and safety of neoadjuvant and primary chemoradiation for women with locally advanced primary vulval cancer compared to other primary modalities of treatment, such as primary surgery or primary radiation, failed to demonstrate any significant difference in overall survival or treatment-related adverse events when chemoradiation (primary or neoadjuvant) was compared with primary surgery. But there were only three publications describing 141 patients, the largest of which (68 patients) was a randomised controlled clinical trial which has only been published in abstract form. (154) This publication had an imbalance in the distribution of patients with inguinal node involvement (node positive patients made up 80% of the primary CRT cohort compared with 62% of surgical patients) and it is not clear whether there was any statistical adjustment for this very poor prognostic factor. There was also no stratification for, or details about, HPV status in the treated population, another important prognostic indicator.

5.3.3 Adjuvant chemotherapy

Adjuvant chemotherapy alone is not routinely undertaken in patients with vulval cancer. There is however increasing evidence for giving chemotherapy concomitantly with radiation in this setting. The evidence for this is discussed above in section 5.2.1. Only 9.1% patients in the largest retrospective study of adjuvant therapies received chemotherapy *following* radiation therapy for node positive vulval cancer. The outcomes for these patients are not reported separately from the larger chemoradiation population where the addition of chemotherapy to radiation resulted in a trend towards reduction in the risk of death (HR 0.81). (137)

5.3.4 Future developments – Targeted agents

Very little clinical work involving targeted biological agents has been undertaken to date in vulval cancer. A recent review of all published evidence of the last two decades in the field, (155) provided a comprehensive insight into the molecular biology of vulval SCC and possible associated molecular targeted therapies. Working groups are mainly focussing on aberrant cell cycle activity as a common pathway in both HPV- and non-HPV- associated cancers. These aberrant cascades are characterized

by an overexpression of p53, Rb and cyclin D1, supporting development of targeted factors of those protein products and of their downstream pathways. Further identified areas of interest are extracellular regulators of cellular activity, such as EGFR, as well as inhibitors of angiogenesis.

HPV-independent vulvar SCC is characterized by actionable mutations, including PI3K, CDKN2A and PTEN as opposed to HPV-associated disease where therapeutic vaccines targeting the E6 and E7 HPV oncogenes and immune-based therapies are under investigation. (155)

A single arm study of erlotinib examined two separate cohorts: 17 patients with locally advanced vulval lesions amenable to definitive surgery or chemoradiation; and 24 patients with metastatic disease (see metastatic section for outcomes of cohort 2). (156) In the first cohort, patients were only treated with erlotinib for between 28 and 42 days. Of these, 35% (6/17) achieved a partial response and four of these six patients had previously undertaken chemoradiation for prior vulval cancer and were being treated for 'in-field' local recurrences. All these patients had high EGFR expression on IHC yet gene amplification, high trisomy or disomy were only found in 35%; there were no identified EGFR mutations. (156)

A recent case report, in one patient with recurrent vulval cancer, using pembrolizumab, a humanized monoclonal antibody targeting the programmed death 1 (PD-1) pathway, demonstrated a complete clinical remission after 2 cycles. Caris next-generation testing revealed a PD-L1 and PD-1 mutation (PD-L1 positive, 2+, 100%). (157)

There is an urgent need to reconsider vulval cancer diagnoses in the light of their aetiology with prospective p16, p53 status in all cases for better management of any background lichen sclerosus and improved prognostication. Additionally, translational research needs to explore the reasons for the poorer prognosis for non-HPV related vulval cancers and novel treatment strategies including biological targeted therapies. In HPV-associated vulvar SCC, novel treatments that exploit and/or enhance the host immune response merit further investigations in line with novel studies for cervical cancer.

Recommendation	Grade of recommendation
Adjuvant (chemo)radiotherapy should ideally take place within 6 weeks of surgery. (Grade B)	
Postoperative radiotherapy is to be considered when:	
- positive excision margins of the primary tumour, and further surgical excision not possible;	Grade D
- pathological margins <2 mm, where repeat excision is not recommended, even though no consensus for the threshold of pathological margin distance exists. Each case should be individualised and discussed at MDT, taking into account patient factors (co-morbidities, previous treatment), location of close margins, and need for groin/pelvic radiotherapy;	Grade D
- presence of >1 metastatic lymph node and/or the presence of extracapsular lymph node involvement.	Grade B
Definitive chemoradiation, generally weekly cisplatin with IMRT, is the treatment of choice in patients with locally unresectable disease.	Grade B
Locally advanced vulval cancer may respond to NACT and could be considered to downstage the local disease and avoid exenterative surgery.	Grade C

Consideration needs to be given to enrolling patients into clinical trials to explore primary chemoradiation (no surgery) alone for patients with earlier stages of locally advanced vulval cancer of HPV origin, to avoid exenterative surgery.	Grade D

Table 12. Recommendations for neoadjuvant/adjuvant treatment of advanced disease at presentation

6 Treatment of recurrent disease

6.1 Recurrence rates and survival

The management of recurrent disease is often challenging and requires a multidisciplinary team approach. A number of factors need to be carefully considered, most notably the previous treatment(s) delivered, the site(s) of disease and the performance status of the patient. The first question to ask is whether further surgery can be proposed without causing mutilating consequences. The patient will also need restaging to confirm that the recurrence is localised (or loco-regional) rather than distant metastatic. Above all, the patient's wishes must be taken into account and this may determine whether radical or palliative intent is the ultimate goal.

Possible options include:
- Further surgery
- Radical radiation therapy with or without chemotherapy
- Neoadjuvant chemotherapy followed by tailored therapy
- Palliative radiotherapy
- Palliative chemotherapy
- Novel approaches including immunotherapy
- Best supportive care

See Table 13 for recommendations in recurrent disease management.

6.2 Localised recurrence

6.2.1 Surgery

Local recurrences should be treated as primary tumours with wide or radical local excision and inguinofemoral lymphadenectomy in case of depth of invasion of more than 1 mm and not previously performed groin dissection or after previous SLN alone in accordance also with the recent ESGO guidelines. (68) Appropriate imaging with MRI and/or CT (and PET CT when radical excision is a consideration) is advised to exclude metastatic disease and determine extent of local disease.
The opinion of an experienced plastic surgeon may often be necessary in order to assess options or local reconstruction and covering of defects in more advanced local relapses, especially since multiple resections may be undertaken over a number of years in patients who have slow patterns of recurrence. When the situation arises that further surgery will lead to a risk of incontinence or a stoma formation, patients may be considered for radical radiation treatment as outlined in section 5.2. Similar discussions will take place regarding the need for "adjuvant radiation therapy" after surgery for relapse and these will be similar to the indications that are used in primary treatment.

6.2.2   Radiotherapy

The indications for postoperative radiotherapy are comparable to those for the treatment of primary disease, even though no randomised studies exist in this setting. (44) Based on evidence from other squamous cell cancers such as cervical and anal cancer, the addition of concomitant chemotherapy should be considered. Definitive chemoradiation is recommended when surgical treatment is not possible. (144)

However, while surgical procedures may be repeated there is usually only one opportunity to give high-dose radiation. The optimal timing of radical radiotherapy must therefore be carefully deliberated; in practice, this is most often scheduled when the surgical options have been exhausted. External beam radiation utilising IMRT or VMAT is the standard approach. A dose to the primary site of 6,000 – 6,400 cGy is recommended; this may be achieved by external beam alone or in combination with either an electron boost or an interstitial implant. (141) This will usually be determined by local resources and expertise.

Where there is a very localised recurrence, of less than 4-5 cm, there is an increasing, although controversial, move towards considering Stereotactic Ablative Radiation Therapy (SABR) as an alternative to IMRT/VMAT. To date there is no evidence to show that this is beneficial but has the advantage that it can be offered by most radiation therapy departments due to a long tradition of experience using interstitial techniques in this setting.

The techniques for radiotherapy for recurrence when used as salvage will be broadly similar to those outlined in section 5.2. There is increasing use of IMRT/VMAT because of the greater precision of identifying the target volume and the potential for reduced toxicity by reducing the dose to the organs at risk (OARs). In addition, it allows the opportunity to give simultaneous integrated boosting doses. As before, concomitant chemotherapy with cisplatin may certainly be considered. The planning of the treatment will again be based on a contrast enhanced CT scan to delineate the vessels and allow identification of the target volume. Discussions may take place as to whether the treatment field should simply encompass the locally recurrent disease at the vulva or whether the inguinal/pelvic nodes ought to be included. Ideally, the nodal basins will be irradiated, especially as the majority of patients will have undergone at least unilateral groin node dissection previously leading to altered lymphatic dynamics. However, this decision may well be influenced by the precise surgical history, including the presence of complications such as lymphoedema, and patient frailty/patient wishes.

Palliative radiotherapy may be used for relapsed disease when surgical options have been exhausted and the patient is not fit for high dose external beam radiotherapy. Simple planning techniques will be used such as parallel opposed fields, and doses between 2000 cGy in five fractions up to 3000 cGy in ten fractions are commonly used. In patients who have bleeding and are of poor performance status, a single fraction of 800cGy or 1000 cGy may be given which can be repeated.

6.3   Palliative chemotherapy

Palliative chemotherapy is to be considered in patients not fit for radiotherapy, or those who have no options of more radiotherapy, nor further surgical excision or those who have distant metastatic disease. Treatment is given with the intention of palliating symptoms to try and improve the quality of life. The most commonly used cytotoxic drugs will include platinum agents, pyrimidines, taxanes and mitomycin-c. Other drugs that may also be considered include gemcitabine and the vinca alkaloids. (148) There have been no randomised trials, but the EORTC GCG reported that single-agent paclitaxel had modest activity in 31 patients with advanced, recurrent or metastatic vulvar carcinoma not amenable for locoregional treatment from ten international institutions. (158) Overall response was 13.8%, while at

a median follow-up of 24 months, median PFS was 2.6 months (95% confidence interval 2.04-4.21). (158)

In patients who are fit, combination treatments could be considered, even though also here large prospective trials are lacking. There is no strong evidence in favour of any particular schedule but regimens such as cisplatin and capecitabine/5-fluorouracil, carboplatin and paclitaxel, and mitomycin-c and 5 fluorouracil/capecitabine may be offered. These regimens will normally be given at 3-weekly intervals up to a maximum of six cycles and with an interval assessment after three cycles to assess the response, in analogy to other gynaecological cancers.

Multiple very small retrospective series of patients are published involving a variety of cytotoxic agents and outcomes. No preferred regimens can be identified from the literature to date. National / international collaboration will be required to identify appropriate treatments for metastatic disease. Two current studies utilise 'biological' agents: a basket study for any gynaecological cancer involves 32 patients receiving durvalumab +/- tremelimumab with stereotactic RT (NCT 03277482 (159)); ten vulval cancer patients have received cisplatin with a p16 based vaccine as treatment for advanced / metastatic disease **(**NCT02526316 (160))

Potentially the most exciting development is coming from new agents such as the PD 1 and PDL 1 inhibitors which have shown significant activity in squamous cancers of the lung and other sites. (157) At present there are phase 1 and 2 studies investigating these drugs in vulval cancer. Other immunotherapeutic approaches are also likely to be rewarding such as tumour infiltrating lymphocytes (TILs) which offer a further approach. (161) Immunotherapy approaches using vaccines and anti-viral therapy may also have a future role.

6.4 Local nodal recurrence

Treatment of groin recurrence is recommended in analogy with a local recurrence where the preferred treatment option is radical excision when possible, followed by postoperative radiation in radiotherapy-naive patients in line with the recent ESGO guidelines.(44) A CT (and PET CT when radical excision is considered) of the thorax/abdomen/pelvis is recommended to exclude distant metastatic disease prior to any local resection. Based on evidence from other squamous cell cancers ,such as cervical and anal cancer, the addition of radio-sensitizing chemotherapy to postoperative radiotherapy could be considered, even though no prospective randomised trials exist in this setting, although limited data do support concomitant cisplatin in primary disease. (44, 144)

Recommendation	Grade of recommendation
Surgical re-excision of local and/ or groin relapse should be considered in patients with relapsed disease amenable to surgery, in analogy with the primary presentation of the disease.	Grade D
Imaging by CT (or PET-CT when appropriate) of the thorax/abdomen/pelvis is recommended prior to any treatment to tailor adequate approaches.	Grade D
In patients not amenable to surgery, palliative chemotherapy, or radiotherapy, or combination of both should be considered, depending on the previous treatment modalities of the patient, her preferences and her fitness status.	Grade C
Systemic treatment may be considered in patients with distant metastases, but published data are insufficient to recommend a preferred protocol.	Grade D

Table 13. Recommendations for treatment of recurrent disease

7 Psychological/psychosexual support

Although this section sits towards the end of the guideline, its principles should be adopted throughout the patients' pathway. It provides information on the psychosocial and psychosexual needs of women following diagnosis of vulval cancer and its subsequent treatments. It aims to guide/signpost the reader to agencies/services that provide appropriate intervention and support for the woman and her family if needed. See Table 14 for recommendations.

Access to specialised psychosexual and psychosocial counselling services is required for women with vulval conditions including, but not limited to vulval cancer.

Women should have the opportunity to address symptoms attributed to their cancer and its management before, during and after treatment. They must have the opportunity to be prepared for the impact of predictable symptoms and issues that may arise as a result of their vulval cancer diagnosis and its subsequent treatments. Both physiological and psychosocial factors can impact on quality of life, addressing possible and actual problems as they arise may help to reduce the negative impact experienced by women.

Predictable short- and long-term effects from treatment include psychosocial concerns; lymphoedema; altered sexual function and body image; and, following radiotherapy, possible altered bowel/bladder function. It is the responsibility of all members of the healthcare team to give women appropriate information at each stage of their care this will ensure informed consent has been obtained. It is good practice to talk about symptoms that could be attributed to cancer and the consequence of treatment at each follow-up appointment and through holistic needs assessment (HNA).

Good quality information is available from both Macmillan, which the patient can source themselves or be given in clinic (this is provided free of charge):

https://www.macmillan.org.uk/information-and-support/vulva-cancer
https://be.macmillan.org.uk/be/s-605-radiotherapy.aspx
https://www.macmillan.org.uk/cancer-information-and-support/after-treatment
https://www.macmillan.org.uk/cancer-information-and-support/impacts-of-cancer/lymphoedema

7.1 Psychosocial

The impact of cancer and treatment can affect quality of life, the psychosocial needs of women should be addressed throughout; holistic needs assessment (HNA) should be performed at pivotal points in the cancer pathway. Women should have the opportunity to explore ways of improving their quality of life through appropriate support and signposting to survivorship/living with and beyond cancer, and psychological services where available.

7.2 Lymphoedema

Risk of developing lymphoedema ranges from 16.7 - 49.2% following lymph node dissection (162) and is significantly worse in women who have both surgery and radiotherapy (163).

Prophylactic information on reducing the risk of lymphoedema should be available to women (https://www.macmillan.org.uk/cancer-information-and-support/impacts-of-cancer/lymphoedema).

Those women who develop lymphoedema should be referred to specialist lymphoedema services for management.

Lympho-vascular anastomosis surgery may be an option for those with severe symptoms, especially in the presence of recurrent cellulitis, although availability of this service is very limited. (164)

7.3 Sexuality/Sexual Morbidity

Women should be fully informed of the anatomical and physiological changes they can expect from treatment and the impact this may have on their sexual function. Some women will not want information regarding sexual function but all should have the opportunity. Information should be factual so women can be prepared and give fully informed consent, however it should be clear for those who want the information that not all women will experience negative changes to their sexuality or sex life; or want help to deal with it. (165)

Addressing the topic will demonstrate that the subject of sexuality is open should she need to seek further information, if difficulties occur. If women experience sexual difficulties, these should be addressed and where possible specific suggestions given e.g. use of lubrication during intercourse, or use of vaginal dilators to reduce the risk of stenosis. (166) Where available, women with ongoing difficulties should be referred to psychosexual services. However, it is strongly recommended that these services *should* be available to all women following a diagnosis of vulval cancer.

7.4 Bowel/bladder function

At follow up ask if any new problems relating to bowel/bladder function, if present initially manage with simple solutions such as loperamide for diarrhoea, dietary changes for constipation, anticholinergics for bladder urgency. Consider referral to other services for persistent problems that are affecting quality of life e.g. gastroenterology, colorectal, urodynamic, continence or urology, as appropriate. (166) A recent Cochrane review found that conformational RT methods help to reduce radiotherapy-related side effects. There was a scarcity of evidence to robustly support the use of any single drug or non-drug option to reduce radiotherapy-related effects on bowel function. They concluded that more high-quality research was required to help inform patients and clinicians how best to manage common pelvic radiotherapy-related side effects. (167)

Recommendation	Grade of recommendation
Specialised psychosexual counselling services should be available to all women with a diagnosis of vulval cancer.	Grade D
All patients should be informed of predictable short- and long-term effects of treatment during the consent process.	Grade D
Patients should receive written information about the disease and management of side effects at appropriate stages of the treatment pathway.	Grade D
All patients should be offered an HNA at key stages of the cancer pathway as part of the Recovery Package to support patients living with and beyond cancer.	Grade D
Referral to other specialist to manage symptoms that affect quality of life should be considered.	Grade D

Table 14: Recommendations for Supportive Care

8 Follow up

8.1 Follow up of VSCC

See Table 15 for recommendations. There are no clinical trial data to inform the follow up strategy in VSCC and strategies are therefore based on expert opinion. (168) VSCC arising on a background of dVIN is more likely to recur than on a background of uVIN (39). In one retrospective review overall VSCC recurrence rate was 22.6%, although the local recurrence rate is proportional to the duration of follow-up, with an annual rate of approximately 4%. The odds ratio (OR) of having a recurrence of VSCC associated with dVIN alone was 3.85 (95% CI 0.52, 28.24) and higher when associated with dVIN in combination with lichen sclerosus/lichen planus (OR 4.3; 95% CI 0.84 to 21.92). The risk of VSCC recurrence of a background of uVIN was much less (OR 1.35; 95% CI 0.20, 9.01). Even in early stage disease, local recurrences can occur a long time after primary treatment, leading some to advocate life-long follow-up after a diagnosis of vulval cancer. (68)

However, those with unifocal, HPV-related disease are at lower risk and the in absence of new areas of uVIN developing during follow up, discharge to primary care, with emphasis on the need for rapid re-referral in the event of developing a new lesion, may be considered after 5 years.

Follow up should include clinical examination of the vulval and groins with assessment for physical and psychological sequelae of treatment. Evidence to inform the optimal follow-up regime in vulval cancer is lacking. Loco-regional rates are highest in the first two years and follow-up regimes should reflect this fact. For uncomplicated early stage disease, intervals of 3-6 months would be reasonable in the first two years, with 6-12 monthly follow up to 5 years. A recent study suggested that three-monthly ultrasound of the groins for two years following negative sentinel node dissection was cost-effective in the detection of lymph node metastasis. (113) For patients with underlying vulval dermatoses, or multifocal/recurrent cancer, more frequent and prolonged follow-up (possibly life-long) may be required. Patient discharged from regular review, should be aware of the need to report symptoms and new lesions at an early stage and should ideally have rapid, direct access to specialist clinics for assessment.

At the first follow-up visit 10-12 weeks post-definitive (chemo)radiation, CT is recommended to document remission.

8.2 Follow up of Basal cell carcinoma of the vulva

Patients with basal cell carcinoma, if margins are clear following surgery, are unlikely to have recurrent disease and long term follow up is not indicated. Patients with Gorlin's syndrome are at risk of basal cell carcinoma across skin sites and so long-term follow up with a specialist dermatology team is more appropriate.

8.3 Follow up of Vulval Paget's Disease

As discussed above the risk of recurrence or development of invasive disease is high and, with lack of data to guide recommendations, long-term follow up in a specialist vulval cancer clinic is suggested. (90)

8.4 Follow up of Vulval Malignant Melanoma.

See the ano-uro-genital mucosal melanoma guidelines for further information (https://melanomafocus.com/wp-content/uploads/2018/05/2_Full-Guideline-V.7.4-FINAL-29.5.18.pdf). (1)

Recommendation	Grade of recommendation
VSCC	
There is no proven regimen for follow up of VSCC. However, recurrence rates/new foci are common, especially on a background of LSA.	Grade D
Those with no recurrence of VSCC or uVIN could be discharged with access to rapid re-referral after 5 years.	Grade D
Those with recurrent disease and multi-focal disease may need life-long follow up.	Grade D
All patients should be told to report new lesions and be seen urgently since interval cancers are not uncommon and should be treated promptly.	Grade D
Vulval Malignant Melanoma	
see https://melanomafocus.com/wp-content/uploads/2018/05/2_Full-Guideline-V.7.4-FINAL-29.5.18.pdf	
Basal Cell Carcinoma	
An initial follow up 3 months following surgery may be appropriate to check healing and local recurrence. Further follow up is not required, if completely excised.	Grade D
Vulval Paget's Disease	
Patients with Vulval Paget's Disease should have long-term follow-up.	Grade D

Table 15. Recommendations for follow up after a diagnosis of vulval cancer.

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