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Expert Opinion

# British Gynaecological Cancer Society (BGCS) vulval cancer guidelines: An update on recommendations for practice 2023

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## Introduction

### *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/. See Supplementary Table 1 and Supplementary Table 2 for details.

Evidence was searched in the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library April 2022, Issue 4), MEDLINE and EMBASE up to April 2022, with top up searches up to July 2023, registers of clinical trials, abstracts of scientific meetings, reference lists of included studies and contacted experts in the field.

This guideline is for healthcare professionals who care for women, non-binary and trans people with vulval cancer and related conditions. Within this document we use the terms woman and women's health. However, it is important to acknowledge that it is not only women for whom it is necessary to access women's health and reproductive services in order to maintain their gynaecological health and reproductive wellbeing. Gynaecological and obstetric services and delivery of care must therefore be appropriate, inclusive and sensitive to the needs of

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those individuals whose gender identity does not align with the sex they were assigned at birth.

The purpose of this guideline update is to collate evidence and propose evidence-based guidelines for the management and diagnosis of adult patients with vulval 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 Guideline [1] for more detailed recommendations. The management of vulval sarcoma is outside of the scope of this guideline.

*Guideline 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.

## Background and epidemiology

Vulval cancer is a rare disease with ~1400 new cases registered per year in the UK during (2016–18), representing less than 1 % of all new cancer cases registered in females. 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]. The incidence in the UK is highest in females over 90 years of age. The incidence of vulval cancer has increased by 17 % since the early 1990s, mainly due to an increase in incidence of over 50 % in those under 60 years [3], and projected to rise by another 5 % over the next 15–20 years [2]. While most vulval cancer is still diagnosed in women aged over 70 years, age standardized rates have increased by over 100 % within the 50–59 cohort between 1993 and 1995 and 2016–2018. 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 2017–19 there were 469 vulval cancer-related deaths per year 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 overall have reduced by 38 % since the 1970s [2], and in the over 70s deaths 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.

Globally, there were 45,240 new vulval cancers in 2020, with an age-standardised incidence rate of 0.85/100,000 females [8]. Incidence rates were highest in Western Europe, at 2.4 per 100,000, although age-standardised mortality is lower (0.49/100,000) than in Eastern (0.89/100,000) and Middle Africa (0.85/100,000).

## Prevention, screening, presentation and diagnosis

*Prevention and treatment of pre-disposing conditions*

For a summary of recommendations on prevention and 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), more commonly referred to as a high grade squamous intraepithelial lesion (HSIL) outside of the UK. Please see below for a description of pathological classification systems. 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].

*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

**Table 1**
Recommendations for prevention and screening.

| 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, surgical excision and laser ablation are treatment options for high grade VIN with similar efficacy. However, cidofovir is currently unlicensed for use in uVIN. | Grade A |
| Good control of lichen planus and lichen sclerosus with maintenance ultra-potent topical steroids improves symptoms and may reduce the incidence of developing SCC. | Grade C |
| There is currently no proven screening test to prevent vulval cancer. | Grade D |
| Women with multi-focal HPV related disease should be followed up with colposcopy of the lower genital tract and digital ano-rectal examination with prompt referral should symptoms of anal cancer develop. | Grade D |
| Women with multicentric 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 symptoms are controlled and confident of self-management, 12-monthly review is suggested. | Grade C |
| Women with lichen sclerosus who develop new focal lesions should be referred to secondary care via a Cancer Wait Pathway if these do not start to respond to nightly ultra-high potency steroids within 1–2 weeks. | Grade C |

significant effect on rates of genital warts and cervical intraepithelial neoplasia in vaccinated populations Bergman et al., 2019 [9]. However, the time to development from exposure is much shorter for benign warts than for usual type vulval high-grade intraepithelial neoplasia (uVIN), the pre-malignant lesion for HPV-related VSCC therefore, 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 pre-invasive 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 [10]. Evidence on the effect of population-level HPV-vaccination on rates of uVIN are expected shortly from a Cochrane review of observational studies [11]. However, in the US, rates of uVIN in adolescent females (aged 15–19 years) have declined by 21 % per since the introduction of HPV vaccination [12]. This is on the background of an increase in HPV-associated vulval cancer by 1.2 % per year, especially in women aged 50–59 years (2.6 %) and 60–69 years (2.4 %) [13].

Studies are ongoing to determine whether HPV-vaccination following diagnosis of uVIN can reduce the risk of recurrence or development of SCC. 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+ [14]). 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 (CI) 22.5 % to 63.2 %) in those vaccinated prior to initial treatment for HPV-related disease, compared to the unvaccinated cohort [15]. Other studies suggest that HPV vaccination after treatment for CIN may reduce the risk of recurrence and other HPV-related disease [16] and RCTs to look at this specifically are on-going. A systematic review of HPV-vaccination in patients treated for HPV-related disease included 16 studies with 21,472 participants randomised to HPV vaccination at the time of surgical treatment versus surgical treatment alone [17]. Whilst the rates of recurrence of CIN2+ and anal intraepithelial neoplasia (AIN) were lower (odds ratio (OR) for CIN2+ 0.31 (95 % CI 0.14 to 0.72; 5 prospective studies; 18,077 participants) and AIN (13.6 % unvaccinated versus 30.7 % vaccinated; P = 0.005;1 study; 202 participants [18], no differences were observed in rates of ano-genital warts (OR 1.04, 95 % CI 0.65 to 1.65; 2 studies; 656 participants) or VIN/VaIN (OR 0.81, 95 % CI 0.42 to 1.55; 2 studies; 740 participants). There is not sufficient evidence to support HPV vaccination for secondary prevention.

*Treatment of uVIN.* A systematic review of the natural history of high-grade VIN (both uVIN and dVIN) found 97 articles including a total of 3,322 women. There was an occult cancer rate of 3.2 % in those with suspected high-grade VIN and 3.3 % went on to develop VSCC during follow up [19]. Of 88 women with untreated high-grade VIN, 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 [20]. 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 [21]. In one small observational study, smoking reduced the response rates to imiquimod, although this association was not seen in a much larger RCT [22,23].

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 to 98.5) versus 71.6 % for imiquimod (95 % CI 52.0 to 84.3)) [24]. Side effects, mainly headache, fatigue and discontinuation due to pain, were slightly more common with imiquimod than cidofovir. Topical cidofovir is currently not licenced for use in uVIN in the UK.

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 [20]. There was little to 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 including photodynamic therapy, Cavitron ultrasonic surgical aspiration and loop electrosurgical excision. There are no published data to support the use of plasmajet.

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 (9to259months). 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. The 2016 American College of Obstetricians and Gynecologists guidelines note that recurrence rates are lower, but still high, if margins are clear (R0 – defined as a 1 mm free margin on microscopic examination) and recommend drawing excision margins of 0.5–1 cm around lesions [25]. However, these guidelines pre-date recent recommendations of more conservative margins with invasive vulval squamous cell cancer and malignant melanoma, and note that this “may be altered to avoid injury to the clitoris, urethra, anus, or other critical structures”. If margins are involved by uVIN, in the absence of invasion within the lesion, options include observation, re-excision or consideration of imiquimod treatment, taking into account the patient’s wishes, general condition and anatomy.

A more recent RCT demonstrated non-inferiority of imiquimod versus surgery for treatment of uVIN [26]. Complete clinical response rates were seen in 37/46 patients (80 %) in the imiquimod group compared with 41/52 patients (79 %) after one surgical intervention (difference in proportion –0·016, 95 % CI –0·15 to 0·18; p = 0·0056). No one treated per protocol imiquimod group developed invasive cancer during the study.

A systematic review of HPV vaccination for the treatment of VIN and vaginal intra-epithelial neoplasia (VaIN) found only seven studies that fit their inclusion criteria. All were case series and at high risk of bias, so the evidence was of very low quality and very uncertain [27].

*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 2.2 and 6.6 % depending on the series [4,28]). A recent systematic review looked at the incidence of developing vulval cancer in women with vulvovaginal LS and LP [29]. They found 14 studies on vulval LS, which included 14,030 women without a previous diagnosis of vulval

neoplasia. During follow-up 2.2 % (range 0 % to 2.7 %) went on to develop vulval cancer,1.2 % dVIN, and 0.4 % uVIN. For those with LP, there were eight studies of 14,268 women; 0.3 % went on to develop vulval cancer, 2.5 % dVIN. Vulval cancer was preceded by dVIN in around half (52 %) of women in one study and the risk of dVIN progressing to invasive disease was 18.1 %, albeit based on only 11 women with dVIN [28,30]. However, these data are not based on population-level data, and lichen sclerosus is frequently under-diagnosed, so these data are likely to be at high risk of bias and 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 %) and maintenance treatment when asymptomatic (e.g., 1-2x weekly) may reduce the risk of progression to SCC [28,29,31,32]. 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, e.g., detergents, such as soap, synthetic underwear, plastic pads, wipes or topical cream/oils.

*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 [33].

*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 [34]). Some studies have demonstrated a 2.6—6.6 % overall risk for those with lichen sclerosus/lichen planus [28,35], which is increased significantly when associated with VIN [4]. A recent systematic review found 31 studies looking at association of VSCC and lichen sclerosus and lichen planus. Due to the heterogeneity of populations and study designs, a narrative synthesis was performed; it is very challenging to give and accurate indication of risk [36]). They found the absolute risk of developing VSCC in patients with lichen sclerosus ranged from 0.0 % (95 % CI 0.0 to 5.52) to 21.88 % (95 % CI 9.28 to 39.97) and was 1.16 % (95 % CI 0.1 to 4.1) with lichen planus [36]. The incidence of VSCC per 1000 person-years for those with a diagnosis of lichen sclerosus ranged from 1.16 (95 % CI 0.03 to 6.44) to 13.67 (95 % CI 5.50 to 28.17) [36]. In contrast, studies have demonstrated 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) [37,38]. 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 [39]. 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 [40,41].

Women with uVIN should receive follow up with formal vulvoscopy. These women are at increased risk of multi-centric disease, so it is important to ensure that they have appropriate assessment of the lower genital tract and perianal area with timely cervical screening. Where anal/*peri*-anal intraepithelial neoplasia is identified a multi-disciplinary approach to follow up and management may be required. There are no published data to support virtual/remote/patient-initiated follow up and use of patient-performed digital photography remain unproven.

The risk of recurrent disease is high, particularly in the first two years [42]. Follow-up regimens should reflect this fact, and increased surveillance is suggested in the first two years, particularly for those with multifocal disease. The optimum follow-up regime remains to be defined, but, in the absence of a robust evidence base, six-monthly follow up for two years and annual follow up to five years is suggested, as a minimum. 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. Human immunodeficiency virus (HIV) testing should be offered as per the 2020 recommendations from the British HIV Association, British Association of Sexual Health and HIV British Infection Society [43].

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 (HIV-positive (HIV + ) men who have sex with men (MSM)), reviewed in [44]. 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 [45]. 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.

*Presentation*

For recommendations on presentation and diagnosis, see Fig. 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 [40]. 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 marsupialisation can delay diagnosis and/or make further surgical treatment more challenging.

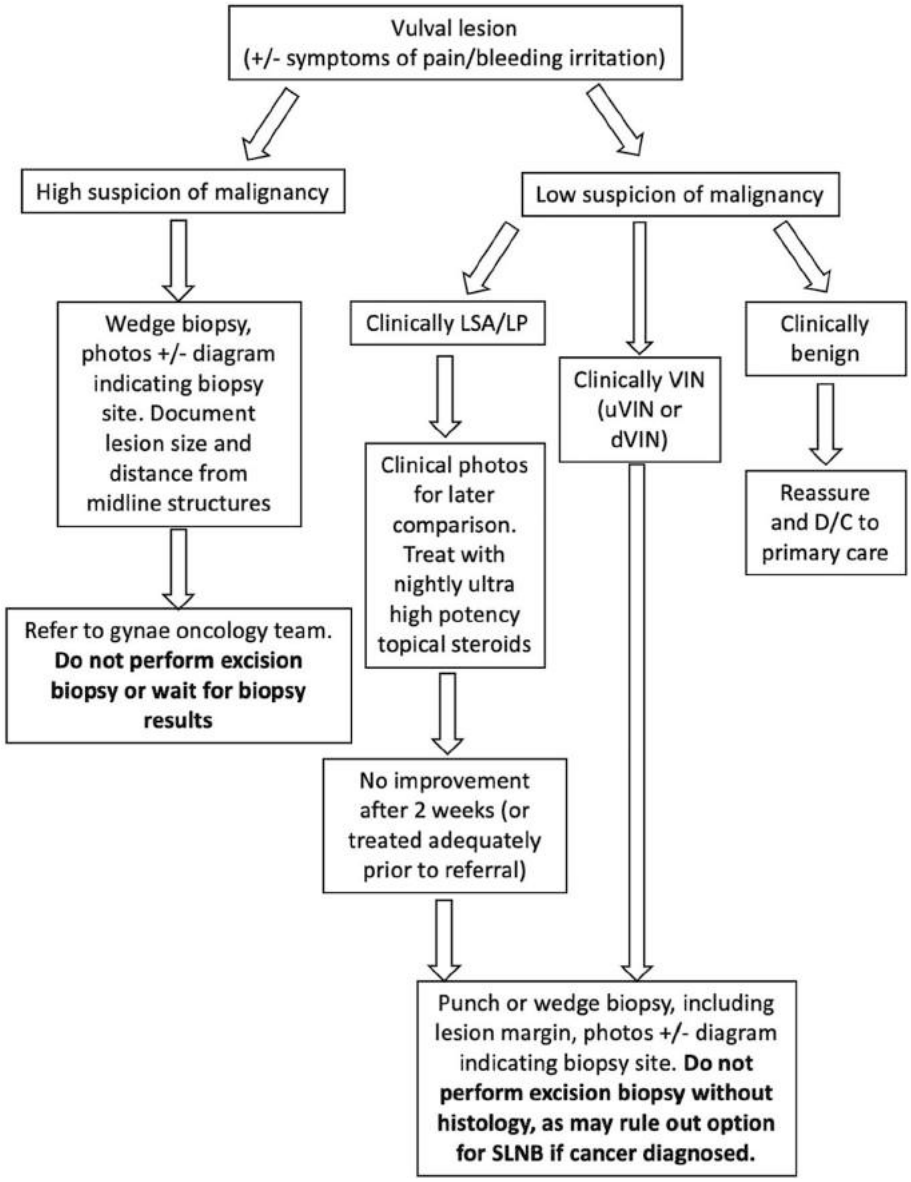


**Fig. 1.** Flowchart demonstrating investigation of suspicious vulval lesion. LSA = lichen sclerosus atrophicus; LP = lichen planus; VIN = vulval intraepithelial neoplasia; uVIN = usual-type VIN; dVIN = differentiated VIN; D/C = discharge.

*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 being 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 is required, indicating each biopsy site is mandatory. 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 ideally also be taken where possible (with a scale indication). This will help to localize the lesion for the treating gynaecological oncologist and assist pre-planning of more definitive treatment. General Medical Council and local guidance on the capture and storage of images 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.

*Pre-operative investigations*

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

*Squamous cell carcinoma (SCC)*

Squamous cell carcinoma most commonly spreads via inguinofemoral (groin) lymph nodes and rarely presents at distant sites, if

**Table 2**
Recommendations for presentation and diagnosis.

| Recommendation | Grade of recommendation |
|---|---|
| Women with suspicious vulval lesions should be referred to a rapid access clinic for urgent assessment, as per NICE guidelines [40,41]. | 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 the diagnosis confirmed by a specialist multi-disciplinary team (MDT) prior to planning radical treatment. | Grade D |

**Table 3**
Recommendations for pre-operative imaging.

| 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 (Ultrasound, MRI or CT) is mandatory to identify potential lymph node metastases. Ultrasound has better specificity and sensitivity in studies, but is operator dependent. | Grade D |
| FNA or core biopsy can be used to evaluate suspicious nodes when this would alter primary treatment, e.g., SLN biopsy. 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 pre-operative 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 |

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 (SLNB), clinical examination and imaging of the groins are required to identify metastatic disease, since obvious groin node involvement would be a contraindication to SLNB.

Ultrasound (USS) has a good accuracy in assessing groin nodes, however, it is operator- and equipment-dependant. In a meta-analysis of ultrasound assessment of groin nodes in patient with vulval cancer, pooled sensitivity of 85 %; specificity of 86 %; positive predictive value (PPV) of 65 % and NPV of 92 % were recorded [46]. 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.

Where tumour encroaches on median structures (urethra, vagina, anus, rectum), imaging should not be limited to just the groin nodes, due to the increased risk of pelvic nodal drainage, and further evaluation of the pelvic nodes with cross-sectional imaging is advised.

Cross-sectional imaging (with computerised tomography of chest, abdomen and pelvis (CT CAP), magnetic resonance imaging (MRI) or single-photon emission computed tomography (SPECT-CT)) can also be used to assess the groin nodes and has the benefit of also allowing assessment of pelvic nodes, which is recommended before undertaking lymphadenectomy.

Staging with full body, cross-sectional imaging (CT CAP) should be considered for all those with suspected or diagnosed with Stage III or greater disease, as the presence of distant metastatic disease will influence the extent of loco-regional treatment options. CT is also suggested for those with locally extensive disease who are not fit for radical treatment, to aid discussion and planning of treatment options.

Due to its high soft tissue resolution, MRI should be considered for tumours with equivocal or clear involvement of midline structures, if this will direct surgical management [47].

Positron emission tomography (PET-CT) is not recommended for the routine staging of vulval cancer. PET-CT has limited value in detecting lymph node metastases less than 5 mm and in necrotic nodes, and inflammatory nodes can be false positive. Sensitivities ranging from 50 % to 100 % and specificities ranging from 67 % to 100 % have been reported in 18F-FDG PET-CT's evaluation of inguinal lymph nodes [48]. There may however be a role for PET-CT if radical surgery is proposed to help to detect pelvic nodal and more distant metastases.

*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].

*Basal cell carcinoma*

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

*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.

*Paget's disease of the vulva*

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

## Pathology

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

*Precursor lesions*

*Vulvar intraepithelial neoplasia, HPV-associated*

HPV-associated neoplasia is the term used in the fifth edition of WHO classification of tumours of the female genital tract [49]. Acceptable terms for describing vulval intraepithelial neoplasia (VIN) include: low-grade squamous intraepithelial lesion (VIN1 or LSIL); high-grade

**Table 4**
Pathology of vulval malignancies and their precursor lesions.

| Pathological subtype | Precursor lesion(s) |
|---|---|
| Vulval squamous cell carcinoma (VSCC) | HPV-associated vulval intraepithelial neoplasia (VIN);HPV-independent vulval intraepithelial neoplasia (dVIN and p53-wild type precursors) |
| Bartholin's gland carcinoma (squamous cell carcinoma (SCC), adenocarcinoma, adenoid cystic carcinoma or transitional cell carcinoma) | HPV-associated VIN in some SCCs |
| Vulval malignant melanoma | |
| Invasive Paget's disease (adenocarcinoma) | Vulval Paget's disease (VPD) (adneocarcinoma in situ) |
| Basal cell carcinoma | |

squamous intraepithelial lesion (VIN2 or HSIL); high-grade squamous intraepithelial lesion (VIN3 or HSIL); VIN2 or 3 of usual type [50].

The terms low-grade squamous intraepithelial lesion (LSIL) and high-grade squamous intraepithelial lesion (HSIL) are not widely used in the UK and the use of the alternative terms low-grade VIN (or VIN 1) and high-grade VIN can be used, with sub-categorisation of the latter as VIN 2 or VIN 3. High grade VIN is characterized by cytological atypia extending beyond the middle third of the epithelium usually accompanied by mitotic activity and lack of maturation of the squamous cells with or without associated stigmata of HPV infection such as koilocytosis.

*Vulvar intraepithelial neoplasia, HPV-independent*

Vulvar intraepithelial neoplasia, HPV-independent, also acceptably described as differentiated VIN (dVIN), 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 *TP53* mutations.

There has been increased awareness of p53 wild type, HPV independent precursors of vulvar squamous cell carcinomas. Differentiated exophytic vulvar intraepithelial lesion (DEVIL) and vulvar acanthosis with altered differentiation (VAAD) are characterized by exophytic growth, acanthotic or verruciform architecture, and an absence of significant nuclear atypia [51]. Recently, there has been a proposal to combine these entities under the term HPV-independent, p53-wild-type verruciform acanthotic vulval intraepithelial neoplasia (HPVi(p53wt) vaVIN) [52]. There is some support for using the term vulval aberrant maturation (VAM) as an umbrella term for lesions that arise in lichenoid dermatitis and lack the atypia needed to diagnose dVIN. These lesions have an unquantifiable risk of subsequent dVIN [53].

*Ancillary imunohistochemistry in vulvar intraepithelial neoplasia*

Although the distinction between HPV-associated and HPV-independent VIN is typically straightforward, morphological overlap between the two can exist [54,55] and create diagnostic difficulty.

Immunohistochemistry for p16, a cyclin dependent kinase inhibitor that accumulates in transforming HPV infection, is mandatory on all index biopsies with a diagnosis of VIN. Block positive staining is a surrogate marker of HPV aetiology and allows accurate distinction between HPV-assocIated and HPV-independent VIN.

Diffuse strong p53 staining of the basal layer with suprabasilar extension has been described in ~85 % of cases of dVIN. [56] Complete loss of staining (null pattern) has also been described [57]. In contrast, normal (wild-type) p53 staining is identified as staining of variable intensity. The different patterns may be difficult to interpret in small biopsy specimens where 'normal' epithelium is not available for assessment. p53 staining is recommended for all cases of VIN, especially when p16 shows non block (mosaic) staining.

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 [58].

*Pathology of squamous cell carcinoma*

*Types of squamous cell carcinomas*

Invasive squamous cell carcinomas constitute 90 % of vulvar cancers. Two pathogenetic pathways exist and correlate with the precursor lesions: an HPV-associated pathway which is associated with younger age, HPV infection and smoking, and an HPV-independent p53 mutated pathway that is associated with older age of onset and lichen sclerosus. There is increasing awareness of an HPV-independent, p53 wild-type pathway often associated with verrucous carcinomas.

*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 [59–61].

*Microscopic features of importance*

*Grade.* Squamous carcinomas of the vulva are no longer graded [60]. This is because the HPV status has far more prognostic significance than the grade. There is no agreed grading system for adenocarcinoma of the vulva.

*Depth of invasion.* This is an independent prognostic factor which, in conjunction with tumour size, helps distinguish between FIGO stage IA and stage IB tumours. Reference to the vulval cancer dataset of the Royal College of Pathologists is recommended for further details [60]. In the updated 2021 FIGO staging system there was a recommendation to change how depth of invasion is measured. Depth of invasion is now "measured from the basement membrane of the deepest, adjacent, dysplastic, tumour-free rete ridge (or nearest dysplastic rete peg) to the deepest point of invasion". This method is associated with less inter-observer variation and early retrospective data suggest that down-staging that occurred as a result of the new measurement guidelines was not associated with increased nodal recurrence [62,63]. This has been implemented in the UK since January 2022. Other guidelines groups, including ESGO, have not adopted the updated FIGO 2021 system, due concerns about low quality and sparsity of evidence to guide clinical decisions about nodal staging [64]. See https://www.rcpath.org/G070-Dataset-for-histopathological-reporting-of-vulval-carcinomas.pdf.

*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 [65].

*Margin clearance.* This is discussed below.

*Preoneoplastic and non-neoplastic disease.* The presence of lichen sclerosus and/or differentiated VIN at excision margins are associated with increased risk of local recurrence [66,67].

*p16 status.* It is increasingly recognised that HPV-associated squamous carcinomas have better outcomes than HPV-independent cancers. Block positive p16 staining by immunohistochemistry is a surrogate marker of HPV aetiology and p16 staining is recommended on all vulval squamous cell carcinomas [68,69]. Documentation of the HPV status of the tumour is strongly recommended (whether HPV-associated or HPV-independent) [49].

*Spread*

*Lymph node metastasis*

The number of involved lymph nodes, the size of the largest metastatic deposit and the presence or absence of extracapsular spread should be recorded. Nodal deposits greater than 2 mm in size have been shown to correlate with poorer survival. In sentinel nodes, it is important to document the exact size of nodal metastases (including the presence of isolated tumour cells) as this will have a direct bearing on subsequent management options [70,71].

*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 below [72]. 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/) [60].

*Definitions of nodal involvement.* The size of the metastases in the lymph node affects the stage. These are defined as per those for FIGO cervical staging [73]:

Macrometastasis: >2 mm pN1;

Micrometastasis: >0.2 mm to ≤2 mm pN1 mi;

ITC – isolated 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 false negative rate of examination of a single H&E slide ranges from 5 to 58.3 % [74], the higher figure due to the additional detection of micrometastases with ultrastaging [75].

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) [76]. Two additional sections are 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.

*Extracapsular spread*

Tumour extension outside the lymph node is an independent predictor of poorer survival and is included in the FIGO and TNM staging systems [61].

*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 unit. 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 [77].

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 and VIN. 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 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 [78].

*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 other cutaneous and non-gynaecological mucosal melanomas, the prognosis is relatively poor (five-year survival is 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 [79,80].

An 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 those from other mucosal sites. BRAF mutations are present in 26 % of vulvo-vaginal melanomas, lower than in other sites, whereas cKIT mutations are found in 22 % of vulvo-vaginal melanomas compared with 8.8 % in other mucosal melanomas. PD-L1 (56 %) and PD1 (75 %) are among the most frequent markers expressed, highlighting the potential use of immunotherapy targeted at this pathway [81].

## Treatment of primary disease

*Surgery*

*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 [61]. For surgical treatment recommendations see Table 6 and Fig. 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 IFLN, but evidence demonstrated no benefit for this technique over radical local excision, with separate incisions for the groin

**Table 5**
Adapted from International Federation of Gynecology and Obstetrics (FIGO 2021) revised staging system [85].

| Stage | Description |
|---|---|
| Stage I | Tumour confined to the vulva |
| Stage IA | Lesions ≤ 2 cm in size, confined to the vulva or perineum and with stromal invasion ≤ 1 mm. No nodal metastasis |
| Stage IB | Lesions > 2 cm in size or with stromal invasion > 1 mm confined to the vulva or perineum. No nodal metastasis |
| Stage II | Tumour of any size with extension to adjacent perineal structures (lower 1/3urethra; lower 1/3 vagina; anus) with negative nodes |
| Stage III | Tumour of any size with extension to adjacent perineal structures(lower 1/3 urethra; lower 1/3 vagina; anus), or with any number of with positive regional (inguino-femoral) lymph nodes |
| Stage IIIA | Tumour of any size with extension to adjacent perineal structures (lower 1/3 urethra; lower 1/3 vagina; anus), or regional lymph node metastasis ≤ 5 mm |
| Stage IIIB | Regional lymph node metastases > 5 mm |
| Stage IIIC | Regional lymph node metastases with extracapsular spread |
| Stage IV | Tumor of any size fixed to bone, or fixed, ulcerated lymph node metastases, or distant metastases |
| | Tumor of any size fixed to bone, or fixed, ulcerated lymph node metastases, or distant metastases |
| | Tumor of any size fixed to bone, or fixed, ulcerated lymph node metastases, or distant metastases |
| | Tumour of any size fixed to bone, or fixed or ulcerated regional lymph node metastases, or distant metastases |
| Stage IVA | Tumour of any size fixed to bone, or fixed or ulcerated regional lymph node metastases |
| Stage IVB | Any distant metastases including pelvic lymph nodes |

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

| Recommendation | Grade of recommendation |
|---|---|
| The excised skin specimen should be secured in a way that allows accurate orientation by the pathologist (e.g., marker suture and pinned to cork board). | Grade D |
| Excision should be planned with macroscopic clearance of tumour with the goal of achieving clear margins (R0) on pathological assessment. | Grade C |
| Optimal radicality (margins) of the excision is unclear. It is acceptable (and often desirable) to limit radicality to preserve structure and function (e.g., preservation of clitoris, anus and urethra) | Grade D |
| Excision margins should be extended superficially to include adjacent differentiated VIN and/or lichen sclerosus to reduce risk of local recurrence | Grade D |
| Discrete multi-focal disease may be managed with multiple wide local excision. Vulvectomy may be required for those with multifocal invasion arising on a background of vulvar dermatosis | 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 for those with large lesions. | Grade D |

lymphadenectomy, which is far less mutilating to women and carries a far lower rate of morbidity and mortality [82,83]. Rates of recurrence in the skin bridge between the positive lymph node and the primary tumour are low [82].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 [84].

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 microscopic margins, including the deep margin (R0). 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 [86–90]. Another contemporary series did not show an association with margin status unless margins were <2 mm [91]. A systematic review of prognostic factors in vulval cancer found a 4 % annual local recurrence rate and that pathological margins <8 mm were not associated with an increased risk [92]. 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 [67,93].

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. To facilitate pathological examination, the excised skin specimen should be secured in a way that allows accurate orientation by the pathologist (e.g., marker suture and pinned to cork board).

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. Recurrence rates if margins are involved with dVIN are high [34,94].

*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, defined by the edge of the tumour lying more than 1 cm from midline structures, such as urethra, clitoris and anus, 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 may be required, 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 without tension. 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.

Multi-focal disease may be managed with separate wide local excisions. Caution is advised in large tumours or those demonstrating multifocal invasion arising on the background of a vulval dermatosis where radical vulvectomy should be considered. The principles of such

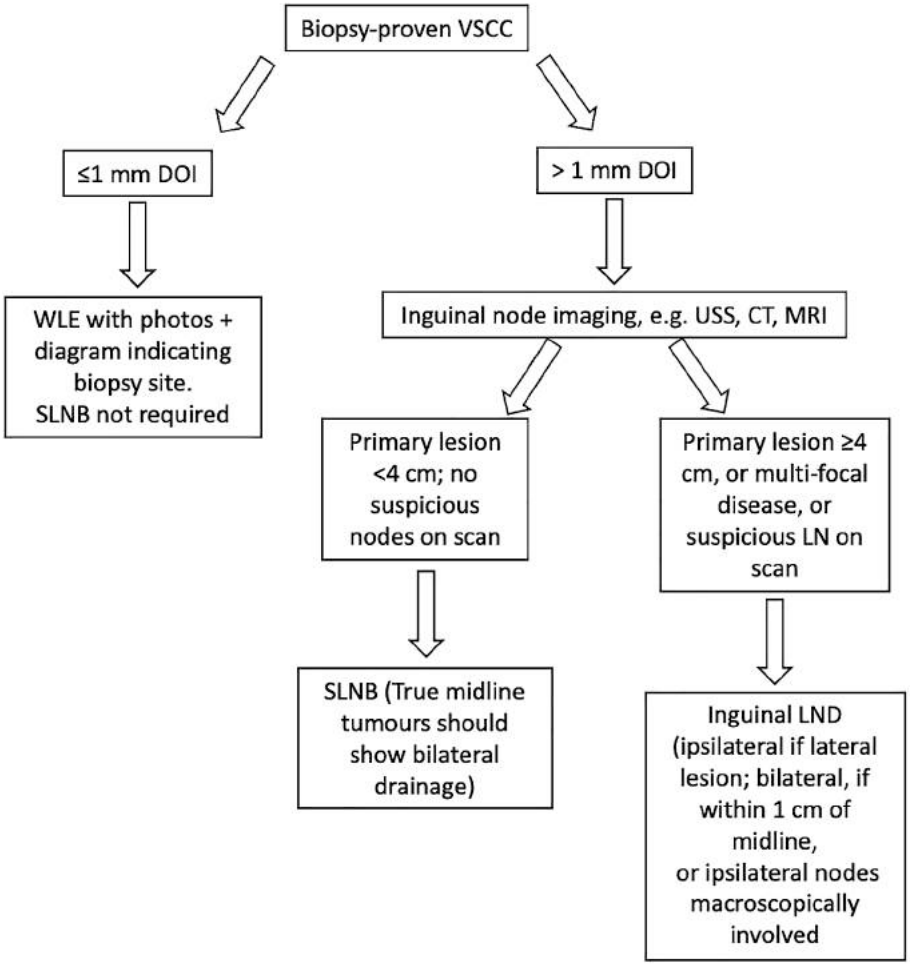


**Fig. 2.** Management of primary lesion. VSCC = vulval squamous cell carcinoma; DOI = depth of invasion; WLE = wide local excision; CT = Computerised tomography scan; SLNB = sentinel lymph node biopsy; IFLND = inguino-femoral lymph node dissection.

surgery are to remove the tumour with microscopically-free margins (R0), 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 below and may involve primary closure or more complex reconstructive techniques [95]. 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. Where the tumour involves the anus, primary treatment with definitive chemoradiation should be considered in an effort to preserve function. Alternatively, downstaging with chemoradiation in a neoadjuvant fashion may allow subsequent surgical excision without loss of faecal continence (see relevant sections below for further details) [96–101]. 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.

*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.

*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, transitional cell carcinoma or adenoid cystic 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 less than 300 cases in the reported literature [102], 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;

**Table 7**
Recommendations for treatment of rare vulval malignancies.

| 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 |
| **Adenoid cystic carcinoma of the vulva** | |
| Adequate surgical excision is key to survival | Grade D |
| In patients with involved resection margins, postoperative radiotherapy can reduce the risk of recurrence | Grade D |
| Distant metastases appear to be relativley common and data to support adjuvant systemic therapies are very limited | Grade D |
| **Vulval Paget's Disease** | |
| Investigations to exclude a co-existing malignancy, e.g., of the breast, gynaecological, urological and colorectal tracts, are only required if there are symptoms concerning for other malignancies. | 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 |
| 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 |

and there should be some normal gland present. The glands and their ducts are comprised of several different cell types: the lining epithelium changes from stratified squamous at the vulval surface to transitional epithelium in the terminal ducts. There can therefore be a variety of histological types of Bartholin gland carcinomas including: adenocarcinoma; squamous carcinoma; transitional cell carcinoma and adenoid cystic carcinoma (see below).

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 are 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 [103]. Due to anatomical constraints, 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 above 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 to 1980, recommended treatment by radical vulvectomy and inguinal-femoral lymphadenectomy (IFLND), similar to other vulval carcinomas [104]. Another series of 36 patients was based on 30 years' clinical experience [105]. 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 IFLND and where indicated, radiotherapy to the vulval and regional lymph nodes. Post-operative radiotherapy reduced the local recurrence rate from 27 % to 7 %. See below for discussion of recommended adjuvant treatment options.

*Adenoid cystic carcinoma of the vulva*

*Background.* Adenoid cystic carcinoma of the vulva is a very rare tumour that arises from Bartholin and Skene glands. It is found more commonly in the salivary glands. There are no RCTs to guide management and treatment is based on case reports and series. Patients with adenoid cystic carcinoma of the vulva should be referred to a specialist MDT.

Adenoid cystic carcinoma accounts for approximately 10 % of all Bartholin's gland malignancies, while Bartholin's gland carcinoma is responsible for 0.1–5.0 % of all vulval carcinomas and 0.001 % of female malignancies. The mean age at diagnosis is 49 years (range 25–80 years) [106].

*Pathological features.* Histologically, adenoid cystic carcinoma is typically composed of rounded islands of uniform malignant epithelial cells with a cribrifom pattern [107]. Pure adenoid cystic carcinomas of the vulva appear unrelated to HPV infection [108]. A recent study showed NFIB gene rearrangements in six out of nine vulval adenoid cystic carcinomas, with two showing a MYB-NFIB fusion pattern [109].

*Spread.* Adenoid cystic carcinomas of the vulva are typically slow growing tumours. They have a propensity for perineural invasion, which may account for symptoms of itching or burning [110]. Spread to lymph nodes is less common than for the more common types of vulval cancer [111]. There is a tendency for local recurrence and distant metastatic spread. The most common site of distant metastasis is to the lungs, however, metastases to bone, liver and brain have also been reported [112].

*Clinical features.* Symptoms of adenoid cystic carcinoma are typically of a vulval lump in the posterior part of the vulva, which may bleed. Other symptoms include pain, dyspareunia, pruritis and discharge from an abscess [106]. The overlying skin may be intact or ulcerated [110]. Due to its rarity and initial clinical similarity with benign cysts it can be misdiagnosed, even as endometriosis, leading to delays in treatment [113,114]. In one series, seven out of 14 patients below the age of 42 years had adenoid cystic vulval tumours diagnosed in association with pregnancy [115].

*Treatment.* There is no consensus on optimal surgical treatment, although the cornerstone of treatment is complete surgical removal [112]. Wide local excision and radical vulvectomy, with or without lymph node removal have all been reported, with recurrence in 68.9 % for wide local excision, compared with 42.9 % for radical vulvectomy [116]. Although radical vulvectomy can reduce local recurrence compared with more simple procedures, it has no impact on rates of distant metastases [110].

For patients with positive resection margins, adjuvant radiotherapy may reduce the incidence of local recurrence [115,117]. A literature review identified 16 patients who received adjuvant radiotherapy; of the ten patients with positive resection margins, none had a local recurrence, but six developed distant metastases [110]. There are fewer reports of primary radiotherapy or chemoradiotherapy, although one case report of a patient who developed multiple local and distant recurrences, in whom radiotherapy achieved complete local control, concluded that adenoid cystic carcinoma of the vulva is radiosensitive [118]. A retrospective review of ten patients with primary Bartholin's gland carcinoma, including two with adenoid cystic carcinoma, treated with radiotherapy or chemoradiotherapy with cisplatin reported three- and five-year survival rates or 71.5 % and 66 %, respectively [119].

Due to the rarity of adenoid cystic carcinoma of the vulva, there is a lack of data from clinical trials of palliative systemic anti-cancer therapy. There are reports of: stable disease after cyclophosphamide, doxorubicin and cisplatin in one patient with lung metastases [116];

stable disease after doxorubicin and cisplatin in one patient with pulmonary metastases; stable disease in a patient who received tamoxifen [110]; and progressive disease in another patient who received both cyclophosphamide, doxorubicin and cisplatin, and ifosfamide single agent for recurrent disease [120]. More recently, a phase 2 study of the multityrosine kinase inhibitor dovitinib in 34 evaluable patients with recurrent or metastatic adenoid cystic carcinoma showed a 6 % partial response rate with 65 % having stable disease at over four months. Sixty-three percent of patients had grade 3–4 toxicity, mostly fatigue and anorexia, and 94 % required dose modification [121]. Further studies are required.

*Prognosis.* The progression-free interval and overall survival are reported as 47 % and 71 % at five years; 38 % and 50 % at 10 years [115].

*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 [122]. Local excision is recommended, with macroscopic clearance; recurrence is associated with involved margins. Surgery should be performed with the aim to achieve margins free of microscopic disease (R0). In a retrospective series of 45 patients, the mean age of presentation was 76 years and most died of other causes [122]. 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 1.11 to 1.73) [123]. 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 anogenital 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 [124]. Cystoscopy, colonoscopy, hysteroscopy, CT and breast examination have therefore been recommended at diagnosis [125]. However, more recent data from the Dutch pathology registry suggests that routine screening for secondary malignancies could be safely omitted for those patients with primary cutaneous VPD as defined by immunohistochemistry [126].

Treatment for VPD consists mainly of surgery ± lymphadenectomy, if there is evidence of ≥1 mm depth of invasion [127]. The updated Cochrane review of treatment of VPD in 2019 noted that there was an absence of evidence in treatment of VPD and that good quality studies were required [127]. Recurrent VPD is common (60–70 %) and is as frequent in those with microscopically clear margins compared to those with involved margins [128]. 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 demonstrated good response rates. These were summarised in a review article that concluded imiquimod seemed to be effective [77]. However, they also noted that treatment schedules differ greatly between the studies 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 [77]. Another systematic review of imiquimod in VPD identified case reports and case series evidence from 63 patients [129]. 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, when surgical margins were clear. In the Paget Trial, a multi-centre prospective observational clinical study from the Netherlands [130], 24 women with VPD were treated with 3-weekly 5 % imiquimod for 16 weeks. The majority (83 %) responded to treatment by the end of the course, with over half (52 %) having a complete response. Side effects of fatigue (67–71 %) and headache (17–46 %) were common and one third of patients reduced treatment to twice a week, and 3/24 discontinued treatment. Of the 12 patients with a complete response, two relapsed with 12 months of treatment and overall, six patients had recurrence after a median of 31 months (14–46months). Whilst response rates are encouraging from these small studies, the data should be interpreted with caution as follow-up periods in the available studies are short, side-effects common and recurrence rates were not based on the gold standard of histology.

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 [77]. However, the certainty of the evidence is very low and risk of reporting bias is very high. In patients with extra-mammary Paget's disease refractory to, or unable to tolerate, imiquimod, an observational study in three women (two with VPD) of a 1:1 mixture of fluorouracil, 5 %, cream and calcipotriene, 0.005 %, cream demonstrated palliation in all three patients and histological response in two, although no complete responses [131].

As with melanoma in situ, the risk of recurrence or development of invasive disease is high (~70 % in one series [128] and, with lack of data to guide recommendations, long-term follow up in a specialist premalignant vulval disease clinic is suggested [132].

*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) [133]. Forty-four patients from the South West of England, with the median age of 71 years, had an overall median survival of 32.5 months (95 % CI 17.8 to 46.5 months) and median recurrence-free survival 12.6 months (95 % CI 7.7 to 17.4 months) [134]. An international study of vulval cancer, VULvar CANcer, involved 100 international centers [135]. 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 %. Tumour size was the only significant prognostic factor for local recurrence ($P = 0.003$). Width of resection margins, lymphadenectomy rate or 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 [136]. 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 [33,137].

Inguino-femoral lymphadenectomy/lymph node dissection (IFLND) has not been shown to improve survival. SLNB 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 [138]. 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 [139].

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 [135]. 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.

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

*Management of inguinal lymph nodes*

*Background.* For recommendations for management of inguinal and pelvic lymph 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 [140,141]. The FIGO staging was updated in 2009 to reflect the impact of size and number of lymph node metastasis on outcome [142]. 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 [142,143]. In light of 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 [144]. 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 [145] means that for this limited group, surgical assessment of the inguinal nodes can safely be omitted. IFLND 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 Fig. 2.

Formal IFLND is associated with high-rates of complications, including wound breakdown and lymphoedema [75]. SLNB should be the standard of care, where indicated, as it is both accurate and associated with reduced morbidity [75,146]. Sentinel node(s) can be identified with vital or fluorescent dyes and radioisotopes [147]. The use of vital dye alone is not recommended due to lower detection rates [72]. The use of combinations of radiocolloid and vital (blue) dye is associated with high detection rates and low groin recurrence rates (<3%) when used to assess unifocal, small (T2, <4 cm) primary tumours [148,149,75]. False negative rates were around 9 % in a *meta*-analysis which included multiple smaller studies [149]. The technique is associated with reduced sensitivity and higher false negative rates for larger tumours [150] and formal IFLND should therefore be standard of care for this group (T3, >4 cm).

Fluorescent detection with indocyanine green fluorescence (ICG) provides a potential alternative to the use of blue dye. When used in isolation, ICG may outperform blue dye, but body habitus may limit the utility of this approach [151,152]. Use in combination with isotope appears to provide comparable accuracy to the combination of isotope and blue dye [153]. As with other methods of SLNB, there is a learning curve associated with the technique [154]. The optimum protocol for ICG use remains to be defined, But it is likely to follow the same principles as injection of other tracers, with intradermal injection at four sites around the tumour prior to node dissection. If using more than one tracer, it is recommended that the same operator injects all tracers used to improve correlation.

Case selection and appropriate training are of paramount importance. Recommended criteria for the use of SLNB in early vulval cancer are listed in Table 9. The European Society of Gynaecological Oncology (ESGO) guidelines [72] 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 and would be highly valuable. This should be centrally funded and co-ordinated, with all cases uploaded by local centres. This could be modelled around other databases in gynaecology in the UK, e.g., https://bsug.org.uk/pages/information/bsug-audit-database/103.

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, bilateral drainage should occur. Where only unilateral drainage

**Table 8**
Recommendations for management of IFLN.

| Recommendation | Grade of recommendation |
|---|---|
| Treatment to the groin(s) is required where the depth of the primary tumour is > 1 mm (>FIGO IA; pT1a) | Grade C |
| Sentinel lymph node biopsy (SLNB) 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 and pathological analysis is possible, and the tumour does not involve the urethra, vagina or anus | Grade B |
| For tumours ≥ 4 cm and/or multifocal disease, inguinofemoral lymphadenectomy (IFLND) via separate groin incisions is recommended | Grade C |
| IFLND 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 (✓) |

**Table 9**
Criteria for performing sentinel lymph node biopsy (SLNB).

| 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 involve urethra, anus or vagina | Representative injection not possible |
| No clinical or radiological evidence of involved nodes | USS ± Cross sectional imaging recommended |

**Table 10**
Recommendations for sentinel lymph node biopsy (SLNB).

| Recommendation | Grade of recommendation |
|---|---|
| Sentinel node dissection is recommended 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 involve the urethra, vagina or anus. | Grade B |
| There is a clear learning curve for SLNB 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 SLNB. 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 (IFLND) should be recommended. | Expert opinion (✓) |
| For tumours involving the midline, bilateral SLNB should be performed. The identification of a unilateral SLN in such tumours should be regarded as 'method failure' and IFLND of the contralateral groin (no sentinel found) is recommended. | Expert opinion (✓) |
| Pathological assessment of the SN should include ultrastaging if the initial sections are negative. Ultrastaging should include serial step sectioning every 200 μm with the use of immunohistochemistry where the H&E sections are negative. | Grade C |
| When macrometastic disease is identified in the SLN, IFLND for the groin affected by metastatic disease is the current treatment of choice, with the addition of radiotherapy as subsequently required. | Grade C |
| For patients with micrometastic disease or ITC detected in the SLN, further treatment with radiotherapy alone (without surgery) is effective and associated with fewer complications than IFLND | Grade C |
| Where bilateral drainage is demonstrated, but metastatic disease is only identified in one groin, the incidence of contralateral metastasis is low and further treatment may be limited to the affected groin, but evidence for this is limited. | Grade C |

is identified for midline tumours, inguinofemoral lymphadenectomy should be performed for the groin in which the technique has failed.

The utility of SLNB in cases of recurrent cancer remains to be defined. The technique appears feasible in this setting [155], but detection rates appear lower and lymphatic drainage may be unusual following previous surgery. Further investigation of the safety and efficacy of the technique in this setting is required.

*Pathological assessment of the SLN.* Intraoperative evaluation and/or frozen sectioning of the sentinel lymph node (SLN) is controversial. There is an increased risk of missing micrometastases on final pathology from the loss of tissue arising from processing for frozen- section assessment [149,156]. A retrospective institutional study provides some reassurance in this regard [157]. However, frozen section confirmation of macrometastases would support proceeding to IFLND at the time of initial surgery. If the initial sections are negative, the SLN 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 [158]. The use of combination detection techniques with pathological ultrastaging is both highly accurate and cost effective in the management of early-stage disease [149,156]. The pathological protocol for assessment of the sentinel lymph node is discussed in detail above.

*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 [70,75].

GROINSS-VII was a prospective phase-II single-arm treatment trial, including patients with early-stage vulvar cancer (diameter < 4 cm) who had surgical treatment (wide local excision with SLN biopsy) [71]. Of the 1213 participants with negative SLN, 31 developed isolated groin recurrence (2.7 % at 2 years, 95 % CI 1.7 to 3.6). If the SLN was involved (metastasis of any size), inguinofemoral radiotherapy was given (50 Gy). The trial design was amended, after the incidence of groin recurrences exceeded their stopping rule, so that those with SLN metastases >2 mm underwent standard of care (ipsilateral IFLND); patients with SLN micrometastases (≤2 mm including isolated tumour cells) continued to receive inguinofemoral radiotherapy. Positive SLN were found in 21 % of participants. In patients with SLN micrometastases, 126 of 160 participants received inguinofemoral radiotherapy; the ipsilateral isolated groin recurrence rate was 1.6 % after 2 years' follow-up. For the 162 participants with >2 mm metastases in the SLN, the isolated groin recurrence rate was 22 % in those who treated with radiotherapy, and 6.9 % in those who underwent ipsilateral inguinofemoral lymphadenectomy ± RT after 2 years' follow-up (P = 0.011). Lymphoedema was uncommon in those who had SLNB alone (4.1 % at 12 months) and less common in those treated with SLN and radiotherapy compared with ipsilateral IFLND ± radiotherapy (10.7 % versus 22.9 % at 12 months). Radiotherapy is therefore a better option than completion IFLND for those with micrometastases in SLN. The ongoing GROINSS-V III study is investigating concurrent chemotherapy and radiotherapy dose escalation for the involved groin as an alternative to IFLND ± RT in case of macrometastasis in the SLN [159],

The management of the unaffected groin in patients with bilateral drainage but unilateral positive SLN is a matter of debate. Early retrospective studies provided conflicting results. Three studies observed contralateral non-sentinel positive node rates of 0 % (0/28), 5.3 % (1/19) and 0 % (0/62), respectively [160–162]. However, another small, single institution study found this rate to be much higher (22 %; 4/18) [163]. Prospective data from the GROINS-V trial group provides reassurance that omitting further treatment to the non-positive contralateral groin may be safe, providing bilateral drainage has been identified for true midline tumours. The authors report on 244 of the 366 patients with a unilateral positive node who received either IFL or no treatment to the contralateral groin. The incidence of a non-sentinel, contralateral metastasis was 2.9 % (7/244; 95 % CI 1.4 to 5.8 %). This rate is comparable to the risk of groin recurrence after identification of a unilateral, negative SLN. The majority of non-sentinel contralateral recurrences occurred in tumours of >3 cm and contralateral treatment would seem wiser for those with bilateral draining primary tumours > 3 cm where the ipsilateral node is positive [164].

*Follow up after SLNB.* The optimal follow-up protocol for detecting groin recurrence in cases of negative SLNB 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 [165]. Recurrence risk is greatest in the first two years [165,166] 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 than clinical assessment, but data to support the cost-effectiveness of routine ultrasound in these patients is limited [167].

*Inguino-femoral lymph node (groin) dissection.* IFLND remains the primary treatment modality for the groins for tumours ≥4 cm. IFLND should include the medial, deep femoral nodes as omission of this group is associated with a higher risk of groin node recurrence [168]. 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 [169,170]. There is no consistent evidence as to the impact of node count on prognosis in vulval cancer [171–174]. 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 [82,175]. 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 [176]. 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 [70,177–179]. Extracapsular spread of tumour is associated with particularly poor prognosis [177,178].

Where inguinofemoral lymph node metastases are identified at lymphadenectomy, adjuvant treatment with radiation is associated with improved survival for cases with >5 mm deposits and/or the presence of extracapsular lymph node involvement [180]. Limiting surgery to debulking of involved groin nodes rather than formal IFLND can reduce the morbidity of dual modality treatment without adverse effect on disease control [181,182]. 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 [72]. 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, as although pelvic recurrence was lower in the surgically treated group, groin recurrence was higher, as radiotherapy (without concurrent chemotherapy) was omitted in this older study [183]. Where bulky pelvic nodal disease is identified, surgical debulking prior to radiotherapy was previously recommended to improve nodal control [72]. Recent developments in radiotherapy mean that it is now feasible to escalate the nodal dose with an integrated or sequential boost. Extrapolating data from the management of squamous cell carcinoma of the cervix would suggest that surgery is not be required when such techniques are utilised [184].

*Complications of lymphadenectomy.* The high incidence of complications (particularly wound breakdown (34 %), lymphocyst formation and lymphoedema (25–45 %) following IFLND has been confirmed in recent studies [75,185]). 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. A population-based cohort study from Sweden demonstrated short-term complication rates of 21.8 %, 39.6 % and 54.2 % after vulval surgery only, vulval plus SLNB and vulval plus IFLND, respectively [186]. Preservation of the great saphenous vein during lymphadenectomy may reduce the risk of cellulitis and lymphoedema and is recommended [170]. Suction drainage is usually employed after IFLND, but the optimum management of wound drainage is yet to be defined Pontre et al., 2018; Thomson et al., 2014 [187–188]. In an observational study, two regimens of suction drainage were compared: volume-controlled (removal once drainage ≤30 ml, after a minimum of 48 h and up to a maximum of 28 days following surgery); versus short drainage (removal after five days following surgery) [189]. They included 77 participants (139groins) for volume-controlled drainage and 64 patients (112groins) for short drainage. There was no difference in wound infection or wound breakdown rates, but there were fewer lymphocysts in the volume-controlled cohort. Overall, complication rates per groin wound were 46 % per groin after volume-controlled drainage versus 75 % after short drainage (RD 29 %, 95 % CI 8 % to 49 %; P = 0.006).

The use of fibrin sealant does not reduce lymphoedema and may increase post-operative infection rates [190]. A small double-blind RCT of 19 patients (38 IFLND), did not find any beneficial effect of using a collagen-fibrin sealant patch [191]. Objective leg measurements over time revealed a prevalence of grade 1 lymphoedema of 44.4 % and 50 % in investigational and control arms, respectively (P = 0.744), and a third (33.3 %) of patients in both arms had grade 2 and 3 lymphoedema in both arms (P = 1). These data suggest that lymphoedema is very common and under-recorded in most studies. 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 [192]. See section below for management of lymphoedema.

A small multicentre RCT of use of energy device, Ligasure™, for dissection and lymphatic sealing during groin node dissection in 20 patients (40 IFLND) found the incidence of one or more complications was 29 % after LigaSure™ versus 70 % after conventional IFLND (using sharp dissection/diathermy) (risk difference 41 %, 95 % CI 19 to 62; P < 0.001) [193]. Patient-reported outcomes of restriction of daily living activities and pain were similar with both treatment methods.

*Recurrent disease after lymphadenectomy.* The outcome following inguinal recurrence after IFLND is historically regarded as poor [194]. Limited recent data suggests that long-term survival can be achieved with multimodality treatment (OS 50 % at 7 years; n = 30) [166]. Restaging with CT/PET 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.

*Reconstructive surgery.* Since the publication of the 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' [132]. The European Society of Gynaecological Oncology Vulvar cancer guidelines also advise 'availability of reconstructive skills for both early & late disease' [72]. 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 and series, and extrapolations from other reconstructive surgery fields. Many 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 and 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 and 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.*

- The resecting surgeon should not be tempted to limit their surgical excision by the constraints of soft tissue closure.
- Where reconstructive surgery is anticipated, 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.
- If the anal margin is involved by the disease, potential approaches are: primary treatment with chemoradiation, 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 and allowing preservation of the anus.
- 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.
- If excision margins are difficult to assess, frozen section should be considered before planning flaps for reconstruction.
- After flap reconstruction, if lateral margins are incomplete then the margin of the flap and 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.

- Skin grafts: split or full thickness skin grafts are useful for skinning vulvectomies where a local flap would be bulkier 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.
- 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.
- 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.
- 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.
- Free flaps: these are rarely used in the vulva because of the diverse local options, but offer the possibility of a more tailored reconstruction.

**Table 11**
Reconstructive options for wound closure.

| Graft and flaps | Pros | Cons |
|---|---|---|
| Split skin graft | Do not 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 abdominus; anterolateral thigh flap | Minimal tension; option to cover large and deeper defects; can be taken from skin outside of previous radiotherapy/ lymphoedema area | Bigger/thicker flap may cause issues and risk of devascularisation; effect on donor sites |
| Free flaps | More tailored reconstruction | Higher risk of devascularisation; effect on donor sites |

*Vacuum-assisted closure (VAC)*

Vacuum-assisted closure or VAC dressings, can be helpful in the management of vulval wounds, but the challenges of obtaining an adequate seal due to local anatomy can limit their utility. 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 [195]. 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 [196].

*Radiotherapy*

Surgery is usually the treatment of choice for vulval cancer, but there are indications for radiotherapy, with or without concomitant chemotherapy, in both the primary, adjuvant and recurrent settings. Table 12 includes the recommendations for adjuvant and primary radiotherapy. The Royal College of Radiologists guidelines on Radiotherapy for Vulval Cancer are in draft and will provide more detail on radiotherapy target volumes, dose fractionation regimens, treatment planning, concurrent chemotherapy and care during treatment. Please refer to this document for further details once published (currently out for consultation).

*Adjuvant radiation / chemoradiation therapy*

Following surgery for vulval cancer, up to 40 % patients develop local recurrence with increasing incidence with time, although many are second primary tumours [92]. The aim of adjuvant treatment is to reduce the risk of disease recurrence but the benefits need to be balanced with the potential long-term consequences of radiotherapy.

Radiotherapy to the vulva is recommended in the post-operative setting, if the surgical resection margins are positive and further surgical excision is not possible [197]. Significant damage/ impairment of structures, such as anus, urethra, and clitoris should be considered when planning surgical re-excision and radiotherapy may therefore be the preferred approach. A dose of 60–64 Gy (equivalent dose in 2 Gy fractions (EQD2)) should be considered with external beam radiotherapy or image guided brachytherapy [198]. In case of close, but clear,

**Table 12**
Recommendations for adjuvant and primary radiotherapy.

| Recommendation | Grade of recommendation |
|---|---|
| Adjuvant (chemo)radiotherapy should ideally take place within 6–8 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 |
| - following inguinofemoral lymphadenectomy, presence of > 1 metastatic lymph node and/or the presence of extracapsular lymph node involvement.<br>- following SLNB: micrometastasis present | Grade B |
| Definitive chemoradiation, generally weekly cisplatin with IMRT, is the treatment of choice in patients with locally unresectable disease. | Grade B |
| 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 to avoid exenterative surgery. | Grade D |

pathological margins, post-operative vulval radiotherapy may be considered to reduce the frequency of local recurrences [199]. There is no consensus for the threshold of pathological margin distance below which adjuvant radiotherapy should be advised, although margins of <2–3 mm have been associated with increased local recurrence rates [200,201,72,91]. Additional factors for local recurrence include lymphovascular or perineural invasion, large tumour size, depth of invasion >5 mm, and presence of LS/dVIN at the resection margin [88,94,202–204]. In addition, a retrospective study of 360 patients with inguinal lymph node involvement reported that delivering radiotherapy to the vulva as well as the inguinal nodes reduced the incidence of local recurrence irrespective of margin status [205].

The GROINS-V II study showed that patients with early-stage disease and a sentinel node metastasis ≤2 mm can be treated with postoperative radiotherapy to the inguinal nodes using a dose of 50 Gy in 25–28 fractions as a less morbid option than inguinofemoral lymphadenectomy [71]. When there is a sentinel node metastasis >2 mm, patients should undergo inguinofemoral lymphadenectomy which is then followed by postoperative radiotherapy in case of 1 or more additional LN metastasis and/or extracapsular tumour spread. In this study the two-year isolated groin recurrence rate was unacceptably high (22 %) with radiotherapy alone using 50 Gy. However, toxicity of radiotherapy versus surgery in this situation needs to be carefully considered on an individual patient basis. The addition of concurrent chemotherapy with radiotherapy may improve outcomes, and the ongoing GROINS-V III study is investigating concurrent chemotherapy with radiotherapy dose escalation instead of IFLND for a SLN macrometastasis.

Probably the most frequent indication for external beam radiotherapy is for patients who have undergone surgical resection and in whom the histological examination has demonstrated positive lymph nodes. Trials conducted by the Gynaecological Oncology Group (GOG) in the 1980s and 1990s showed that adjuvant radiation therapy was of benefit if there were two or more lymph nodes involved, or if there were one or more nodes with extracapsular spread [183]. A more recent database study of 2779 patients with involved lymph nodes showed adjuvant radiotherapy improved survival for patients with a single involved node, as well as for those with two or more nodes, compared to no further treatment [206]. The addition of chemotherapy to radiotherapy further improved outcomes, with five-year overall survival of 49 % when two or more lymph nodes are involved compared to 29 % with radiotherapy only and 21 % for no adjuvant treatment [204,206,207].

External beam radiotherapy should be delivered with intensity-modulated radiotherapy techniques (including volumetric modulated arc therapy (VMAT)), which reduce dose to the organs at risk, as well as providing the option of dose escalation with an integrated boost to involved nodes that should improve outcomes [208,209]. Treatment should ideally be commenced within eight weeks of surgery and completed within 105 days as overall treatment time impacts on outcomes [210].

*Primary chemoradiotherapy*

Primary radiation therapy should be considered for patients deemed inoperable due to extent of tumour, when exenterative surgery with permanent stoma formation would otherwise be required, and/or unfit for anaesthesia. Early studies assessed the role of neoadjuvant chemoradiotherapy prior to surgery, with the GOG completing two landmark multi-centre phase 2 trials; GOG 101 delivered 47.6 Gy with a split course schedule [211]; and followed by GOG 205 which delivered 57.6 Gy without any treatment gaps. These studies reported higher complete clinical (64 % versus 48 %) and pathological response rates (50 % vs. 31 %) with the higher dose [212]. Of those who achieved a complete clinical response, 78 % had a pathological complete response.

With more advanced radiotherapy techniques enabling further dose escalation, the treatment aim should now be to deliver definitive treatment, with surgery reserved only for patients without a complete response. A case series using IMRT to escalate vulval dose to median 66 Gy and involved nodes to 60.6 Gy and concurrent weekly cisplatin chemotherapy had a complete clinical response rate of 88 %, compared to 63 % with median vulval dose of 59.4 Gy pre-operatively [213]. A large database study of >2000 patients showed that patients receiving definitive chemoradiation to a dose above 55 Gy had equivalent survival to those receiving surgery after RT [214]. The five-year survival was 50 % with chemoradiation compared to 27 % with radiotherapy alone in a National Cancer Database study of 1352 patients, with a significant survival benefit still present when propensity matched to account for age [215]. A recent multi-centre study of 52 patients delivering 64.8 Gy to the primary tumour and concurrent capecitabine chemotherapy had a complete response rate of 62 % at 12 weeks, and persistent response at two years of 42 %, with five-year overall survival 52 % [216]. The acute and long-term toxicity was acceptable, with grade 3 long term toxicity in 21 % patients.

Staging investigations should include MRI and CT-PET scans to aid radiotherapy planning. The target volume should include the primary tumour, vulva, inguino-femoral and pelvic nodes depending on extent of disease. Please refer to the new Royal College of Radiologists vulval cancer radiotherapy guidance once published (currently out for consultation).

IMRT techniques are recommended, with integrated or sequential boosts to escalate dose to macroscopic disease to at least 64 Gy (EQD2) to primary tumour. MRI-image guided brachytherapy may be considered as a boost for selected patients.

Treatment breaks should be avoided with treatment completed within 50 days when possible. Careful management of acute toxicities is essential, with regular clinical review, expert skin care and adequate analgesia. Assessment of response should be performed at 12 weeks following completion of treatment with clinical assessment and imaging. Biopsy should be performed if residual disease is suspected.

*Palliative radiotherapy*

Palliative radiotherapy can provide symptomatic benefit when radical radiotherapy is not an option. 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 include 20 Gy in five fractions or 30 Gy in 10 fractions delivered over one or two weeks, and hypofractionated regimens to a smaller volume including 30–36 Gy

in six fractions over three to six weeks. In very frail patients who have active bleeding, a single fraction of 8 Gy or 10 Gy may be considered and this can be repeated if required.

*Chemotherapy*

See Table 12 for recommendations for adjuvant/neoadjuvant treatment.

*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 below. The potential for using more targeted systemic therapies e.g., growth factor receptor inhibitors, biological agents and immunotherapy is also explored here.

*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 and 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 [101,217]. Reported long-term survival was limited, e.g., 24 % still alive at 3 years [97]. 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 to 100 %. [99,100] 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 [218]. Another recent publication describes the use of platinum-based NACT or bleomycin alone in 32 and five patients, respectively [96]. Responses were documented in 30 patients (81 %) and 27 proceeded to radical vulvectomy. Eleven women (40 %) had residual tumour in IFLN 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 [219]. 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 vulval cancer [99,211,219].

In analogy to the standard carboplatin and paclitaxel regimen given in other gynaecological cancers, 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 [220]. 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 [221]. 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 five-year overall survival (73 %) than definitive CRT (43 %) alone. However, no significant difference was found between CRT (five-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 five-year overall survival (67 % vs. 20 %, P = 0.001). The authors concluded that NAC plus surgery can potentially improve survival of patients with advanced vulval cancer.

A Cochrane review [222] 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 [223]. 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.

*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. 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 non-significant reduction in the risk of death [206].

*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 [224], 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 vulval 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 [224].

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) [225]. 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 [225].

There is an urgent need to reconsider vulval cancer diagnoses in the light of their aetiology with prospective p16- and 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 vulval SCC, novel treatments that exploit and/or enhance the host immune response merit further investigations in line with novel studies for cervical cancer.

*Treatment of recurrent disease*

The management of recurrent disease can be challenging and may require 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 treatment of recurrent disease may be associated with significant morbidity and often impacts on bladder, bowel and sexual function. As always, the patient should be central to treatment planning and a clear decision made as to whether intervention planned is with radical or palliative intent.

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.

*Vulval recurrence*

*Surgery.* Vulval 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 ESGO guidelines [64]. 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 use of repeat SLNB alongside radical excision of small recurrences/second tumours is discussed above Data to support the safety/efficacy of SLNB in the setting of recurrent disease are very limited, based on one small retrospective study [205]. Prospective studies are ongoing to provide data on oncological safety but until more data are available, repeated SLNB is not advisable.

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 above. 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.

*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 [72]. The addition of concomitant chemotherapy should be considered in the similar approach for primary disease.

Definitive chemoradiation is recommended when surgical treatment is not possible or would result in a permanent stoma [212]. While surgical procedures may be repeated there is usually only one opportunity to give high-dose radiation so 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 60–68 Gy is recommended; this may be achieved by external beam alone or in combination with either an electron boost or an interstitial implant [209].

The techniques for radiotherapy for recurrence when used as salvage will be broadly similar to those outlined above. 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. There may be a role for re-irradiation with either EBRT, stereotactic radiotherapy or brachytherapy for selected patients if no further surgery is feasible.

Although isolated distant recurrence is rare, stereotactic radiotherapy or surgery can be considered for patients with oligometastatic disease.

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 may be used, and doses between 20 Gy in five fractions up to 30 Gy in ten fractions are commonly used. A higher dose may be feasible using an IMRT approach including 30–36 Gy in 6 fractions. In patients who have bleeding and are of poor performance status, a single fraction of 8 Gy or 10 Gy may be given which can be repeated.

*Systemic therapies.* Palliative chemotherapy is to be considered in patients for whom further surgery or radiotherapy is not feasible (either due to fitness or previous treatment) or for 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 [218]. 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 [226]. 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) [226].

**Table 13**
Recommendations for treatment of recurrent disease.

| Recommendation | Grade of recommendation |
|---|---|
| Surgical re-excision of local and/ or IFLN 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 |
| SLNB can be considered for recurrent disease, if the new focus of invasion meets criteria for primary SLNB. Data regarding the safety and efficacy of this approach is very limited | 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, the patient's preferences and the patient's 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 |

In patients who are fit, combination treatments can be considered. 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 three-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 studies utilised 'biological' agents. A basket study for any gynaecological cancer was due to involve 32 patients receiving durvalumab ± tremelimumab with stereotactic RT (NCT03277482) [227]). This study was terminated after 16 patients were recruited due to no responses in non-irradiated lesions. Eleven vulval cancer patients have received cisplatin with a p16-based vaccine as treatment for advanced / metastatic disease (NCT02526316 [228,229]); results have not been published, although this study competed some time ago.

Immunotherapy agents, particularly checkpoint inhibitors, have shown significant activity in squamous cell carcinomas including cancers of the cervix, skin and lung [230,231]. Pembrolizumab, a humanized monoclonal antibody targeting the programmed death 1 (PD-1) pathway, demonstrated a complete clinical remission after 2 cycles in a case study lung [231]. The phase 2 multicohort, open-label KEYNOTE-158 study enrolled women with advanced VSCC with prior treatment failure to receive pembrolizumab 200 mg i.v. 3-weekly, for up to 35 cycles [204]. Overall, the objective response rate (ORR) was 10.9 % (95 % CI 5.6 % to 18.7 %), 9.5 % (95 % CI 4.2 % to 17.9 %) in 84 patients with PD-L1-positive VSCC, and 28.6 % (95 % CI 3.7 % to 71.0 %) in the seven patients with PD-L1-negative VSCC. Median PFS was 2.1 months (95 % CI 2.0 to 2.1 months) and OS 6.2 months (95 % CI 4.9 to 9.4 months). Treatment-related adverse events occurred in half of the patients (50.5 %) and serious adverse events (grade 3–5) in 12 %). Two of the 101 patients died from treatment-related hepatitis. Data for vulval cancer are very limited, mainly as a result of the low incidence of the disease. Extrapolating data from the management of squamous cell cancer of the cervix, the addition of pembrolizumab in cases with PD-L1 expression with combined positive score (CPS) $\geq 1$ and/or bevacizumab to platinum-based chemotherapy may be considered for selected patients in first line, although these drugs do not have specific approval for vulval cancer.

Other immunotherapeutic approaches are also likely to be rewarding such as tumour infiltrating lymphocytes (TILs) which offer a further approach [232]. Immunotherapy approaches using vaccines and antiviral therapy may also have a future role.

*Regional nodal recurrence.* Treatment of IFLN recurrence is recommended in analogy with a local recurrence where the preferred treatment option is radical excision followed by postoperative chemoradiation in radiotherapy-naive patients [72]. Re-staging with CT/PET-CT is recommended exclude distant metastatic disease prior to any local resection. In an analogous fashion to the treatment of primary disease, limiting surgery to debulking of large nodes prior to planned chemoradiation may be considered to reduce morbidity without affecting disease control [181,182]. Although historic data suggest IFLN recurrence is associated with a poor outcome [194], the use of multimodal treatment can provide long term survival in up to 50 % of selected patients [166].

## Supportive care

Although this section sits towards the end of the guideline, its principles should be adopted throughout the patient's 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.

Patients should have access to personalised care including holistic needs assessment, a care plan and health and wellbeing information in line with the NHS Long Term Plan [233], similar strategies in the devolved nations and Macmillan's guidance on providing Personalised Care for People Living With Cancer [234].

Determining appropriate strategies for supporting cancer survivorship should be based on three key elements: physical, psychosocial and psychosexual. Supporting cancer care has proven effective in improving physical function, fatigue, anxiety and depression in other cancer types [235]. The challenge remains to implement this effectively in vulval cancer patients, where the disease is often multi-faceted. It is recognised that there are potential cost savings if survivors are effectively able to self-manage, reducing the overall burden on the healthcare system [236].

Supportive care should also try to encompass preparation for treatment (prehabilitation) which has been proposed to improve outcomes in gynaecological surgery [237], although a standardised, well-evidenced programme does not yet exist [238].

Both physiological and psychosocial factors can impact on quality of life, and addressing possible and actual problems as they arise, may help to reduce the negative impact experienced by gynaecological cancer patients [239]. It is good practice to talk about symptoms that could be attributed to cancer and the consequence of treatment, this should also be addressed at each follow-up appointment or through holistic needs assessment (HNA). Since longer-term survivorship care is becoming increasingly important in the overall well-being of women treated for vulval cancer, effort should be made to introduce nurse or allied health practitioner (AHP)-led survivorship clinics to support holistic and individualised approaches.

Women should have the opportunity to address symptoms attributed

**Table 14**
Recommendations for supportive care.

| Recommendation | Grade of recomendation |
|---|---|
| All patients should have a named keyworker to co-ordinate treatment and their care pathway and be give contact details in a format they can understand | Grade D |
| Access to a CNS or equivalent and psycho-sexual counsellors should be available as part of the multi-disciplinary team. | Grade C |
| Written information should be provided about treatment choices and side effects including late effects. | Grade D |
| Recording of late side effects should be documented | Expert opinion (✓) |
| Patients who develop lymphoedema should be referred to specialist lymphoedema service for assessment and management | Grade D |
| Patients with signs of radiation induced proctopathies or enteropathies should have access to care from a team of professionals who may include oncologists, gastroenterologists, bowel surgeons, therapeutic radiographers, dieticians and specialist nurses. | Grade D |
| Patients with troublesome urinary symptoms after treatment should have access to urology and specialist continence services for assessment, diagnosis and conservative treatment. | Expert opinion (✓) |
| Patients should be counselled regarding the increased risk and symptoms of pelvic insufficiency fractures, early menopause and infertility if appropriate, and the risk of treatment related neuropathies. | Expert opinion (✓) |
| Hormone replacement therapy for SCC vulval cancers is not contraindicated and should be assessed on an individual basis. The overall evidence does not support or contradict HRT use in patient with melanoma, and advice should be individualised | Expert opinion (✓) |

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.

Good quality information is available from both Macmillan and Eve Appeal charities. The challenge is for providers to look to offer innovative ways of offering such services to those with vulval cancer. Patients who experience late effects of their cancer treatment will require continuous and new information about how to best manage symptoms. Consideration should be given to online clinics, webinars and face-to-face clinics delivered by CNSs and Cancer Support Workers.

Patient resources: macmillan.org.uk/cancer-information-and-support/vulval-cancer and eveappeal.org.uk/gynaecological-cancers/vulvar-cancer.

*Psychosexual*

Psychosexual issues following vulval cancer are common and difficulties include increased vaginal dryness, dyspareunia, reduced arousal and desire, altered orgasm and sexual satisfaction, and reduced pleasure [240]. Women also experience psychological challenges around their sexuality in relation to altered body image, femininity fertility and loss of role [241]. A recent study showed sex and body image are major concerns in patients diagnosed with vulval cancer, nearly one in three women diagnosed were afraid to have sex [242]. Although treatments do not always result in higher risk of sexual dysfunction, especially minimally invasive approaches [243,244], the risk increases with addition of radiotherapy, with up to 81 % patients reporting sexual difficulties including dyspareunia, vaginal stenosis, reduced desire and arousal [245]. The use of vaginal dilators or vibrators following radiotherapy should be recommended to reduce the risk of stenosis [246].

Factual information on possible changes to sexual function due to surgery, radiotherapy and chemotherapy should be given to the patient prior to treatment, to acknowledge that the subject of sexuality is open should she need to seek further information, if difficulties occur [247]. Access to specialised psychosexual and psychosocial counselling services is recommended for women with vulval conditions including, but not limited to vulval cancer.

Sexual difficulties have multifaceted causes including physiological/biological, psychological, interpersonal and socio-cultural factors, so a joint approach to addressing problems should be adopted, having a multi-disciplinary approach to allow clinicians the safety to address this topic and refer to on if the issues are beyond their comfort or expertise [240,248].

Assessment and identification of sexual issues by clinicians can be done efficiently and easily with short validated tools using a style of inquiry which starts by acknowledging how common sexual dysfunction is amongst cancer survivors rather than asking direct questions [248]. Assessment tools/patient reported outcome measures (PROMS) can help to identify sexual difficulties, promote discussions and management of sexual issues [249–251].

If sexual difficulties are present these should be addressed and where possible specific suggestions given, e.g., psychosexual education, use of lubrication during intercourse or vaginal moisturiser [240,252,253]. Where available, patients with ongoing difficulties should be referred to psychosexual services especially in women when sexual difficulties are persistent despite appropriate interventions and where there are high levels of individual/couple distress, the woman has pre-existing sexual problems and psychological vulnerability prior to diagnosis, or if there are dual sexual difficulties within the relationship.

Patient resources: Female pelvic side effects and your sex life | Macmillan Cancer Support. https://www.macmillan.org.uk/cancer-information-and-support/treatment/coping-with-treatment/your-sex-life/side-effects-of-treatment-to-the-female-pelvic-area

*Psychosocial*

The impact of cancer and treatment can affect quality of life, the psychosocial needs of patients should be addressed throughout. A HNA should be performed at pivotal points in the cancer pathway. Patients should have the opportunity to explore ways of improving their quality of life through appropriate support and signposting to living with and beyond cancer services, and psychological services where available.

Patient resources: macmillan.org.uk/cancer-information-and-support/after-treatment.

*Lymphoedema*

Lymphoedema can affect lower limbs, lower abdomen and the pelvis/perineum after vulval cancer treatment. Risk of lymphoedema after IFLND ranged from 17 to 50 % [254,255]. However, the lack of a standardised definition of lymphoedema and its measurements make true evaluation difficult [256]. The increasing use of SLNB rather than IFLND should reduce incidence [75]. Lymphoedema is significantly worse in women who have both surgery and radiotherapy [257]. High BMI, lack of physical activity and pre-existing lymphoedema may also increase risk [185].

Prophylactic information on reducing the risk of lymphoedema should be available to patients. Pre-surgical assessment, regular monitoring and early intervention may have some benefit in reducing the burden of lymphoedema in gynaecological cancer patients [258]. See macmillan.org.uk/Lymphoedema for patient resources. Patients should be made aware of overt signs of lymphoedema; swelling, changes in sensation, aching, skin changes. Prophylactic monitoring with bioelectrical impedance analysis may be able to detect sub-clinical signs of lymphoedema [259].

Those patients who develop lymphoedema should be referred to specialist lymphoedema services for assessment and management of this condition. Management can include compression garments, manual lymphatic drainage and pneumatic compression [260]. Patients should be encouraged to maintain a healthy weight, keep active and undertake daily skin care. Lymphaticovenular anastomosis (LVA) surgery may be an option for those with early stage lymphoedema [261], especially in the presence of recurrent cellulitis. Evidence is growing that early intervention with LVA may reduce the incidence of lymphoedema in gynaecological cancers [262]. In a small, single centre study, immediate lymphatic reconstruction in vulval cancer patients with inguinofemoral node dissection had a 17 % reduction in lower limb oedema [263]. Currently, availability of LVA service is very limited [262,264].

*Management of late effects of radiotherapy*

Late effects, especially from radiotherapy are often permanent and progressive and can manifest many years after treatment completion. Patients and primary care teams should be made aware that beyond the conventional follow up period they can be seen in a clinic to investigate late effects as well as potential recurrences. The following sections are generic to patients treated with pelvic radiotherapy and are not specific to those treated for vulval cancer.

Late side effects in gynaecological cancers are dependent on treatment modality and potentially pre-existing morbidities [265]. Consequences of vulval cancer and its treatment and can include lymphoedema, effects on gastrointestinal and genitourinary systems, bone pain/insufficiency fractures and nerve damage.

Professional resources: PRD Best Practice Pathway - PRDA

*Gastrointestinal late effects*

Gastrointestinal (GI) effects from radiotherapy can include faecal urgency, diarrhoea, leakage, rectal bleeding, malabsorption syndromes,

ileus/obstruction and small bacterial overgrowth. Data are not adequate to define how many patients experience permanent GI changes post gynaecological cancer treatments [266]. There is limited evidence to support the use of prophylactic dietary or pharmacotherapy interventions to reduce GI toxicity from pelvic radiotherapy [267], although a recent systematic review and *meta*-analysis concluded biotic supplements may reduce acute GI toxicities [268].

At follow up it is important to ask if there are any new problems relating to bowel function. Validated tools can be used to assess symptoms include: EORTC PRT23 for radiation proctitis [269]; or ALERT B [270]. European Organisation for Research and Treatment of Cancer is currently developing a vulval cancer PROM [271].

GI symptoms following pelvic cancer treatment are complex and multifactorial. They should be managed in a sequential manner using a validated algorithm [266,272]. Initial management may involve simple lifestyle advice and medicines such as loperamide for diarrhoea and dietary changes for constipation. A Cochrane review of non-surgical options such as sucralfate for rectal bleeding look promising but the quality of evidence remains very low [273]. More complex and persistent problems warrant referral to specialist services e.g., gastroenterology, colorectal, dieticians. A small study showed Sacral Nerve Stimulation (SNS) can improve faecal incontinence following pelvic radiotherapy without increased complication rates [274]. Trials investigating the use of hyperbaric oxygen treatment to treat chronic gastrointestinal radiation damage do not provide sufficient data to be conclusive [275].

Professional resources: Managing lower gastrointestinal problems after cancer treatment | Macmillan Cancer Support.

Patient resources: Bowel problems after pelvic radiotherapy - Cancer treatment | Macmillan Cancer Support.

*Urinary late effects*

Gynaecological cancer patients have increased levels of urinary system disorders [276]. Stricture, contraction, obstruction, inflammation, impaired pelvic floor function and detrusor over-activity are potential consequences of treatment. High grade (3and4) toxicities appear to be rare in vulval cancer patients 12 months after treatment [71] or at 34 months [215], although longer-term data are lacking and radiation-induced fibrosis, which can cause urinary dysfunction, can occur may years after treatment.

Improved delivery of radiotherapy treatments to spare structures of the urinary system may reduce late effects [277]. Evidence for pharmacological interventions is lacking.

Urinary incontinence is common, affecting up to 40 % of the UK female population and becoming more prevalent with age and postmenopause [278]. It is therefore useful to establish a baseline for urinary function prior to any treatment [277] although there is no agreed validated tool to use. Enquire directly about any new problems relating to bladder function at follow up visits.

Treatment for increased urinary frequency, urgency and stress incontinence can include coping strategies, absorbent containment products, pelvic floor muscle re-education and bladder retraining [279]. Conservative pharmacotherapies and treatments such as antimuscarinics and bladder instillations may be preferable, as surgical interventions have high failure rates due to tissue ischaemia [280,281]. Patients may benefit from discussion at a urogynaecology MDT. Complex problems such as fistulae, haematuria and radiation induced interstitial cystitis require intervention from urology specialists. Hyperbaric oxygen therapy may have some benefits for late radiation cystitis [282].

Patient resources: Managing bladder late effects | Macmillan Cancer Support.

*Endocrine late effects*

Pelvic radiotherapy significantly increases the risk of pelvic insufficiency fractures (PIF) in older women [283] and patients should be counselled regarding the increased risk and symptoms of pelvic insufficiency fractures. PIF occur under normal stresses on bones weakened by external beam radiotherapy. Recent *meta*-analyses of gynaecology pelvic radiotherapy patients reported PIF rates of 7.8 % to 15.3 % treatment; developing 7 to 39 months post treatment, with the majority occurring within 2 years of treatment [284–286]. Pain is the main reported symptom although up to 40 % may be asymptomatic [286].

Pre-treatment screening for PIF risk factors including bone density measurements, fracture risk assessment tool, age >65 years, low BMI 20 kg/m$^2$, history of fragility fracture, oral corticosteroid use and smoking history are probably warranted in post-menopausal gynaecological cancer patients [284,287]. Interventions to prevent PIF such as calcium and vitamin D supplementation, bisphosphonate therapies, or denosumab have little evidence but warrant further investigation [288,289]. Strategies to prevent fractures in these patients, such as the use of IMRT may benefit this population at significant risk of PIF but data is not conclusive [284,286].

Patients should be made aware that pelvic pain, pain on weight bearing and immobility are signs of PIF [286]. MRI images are useful to diagnose PIF and distinguish between bony metastases [290]. Conservative management involves rest, pain management and physiotherapy led exercise for stable fractures.

Professional resources: Endocrine late effects guidance for healthcare professionals | Macmillan Cancer Support.

Patient resources: Bone health and looking after yourself | Macmillan Cancer Support.

Pelvic radiotherapy damages oocytes at low doses, can lead to uterine changes and induce the menopause. Early menopause increases osteoporosis and cardiovascular disease [291]. Ovarian transposition in pre-menopausal patients has been documented for colo-rectal cancers and cervical cancers prior to pelvic radiotherapy, although data are lacking for vulval cancer patients and the majority of patients are post-menopausal.

Systemic anti-cancer therapies and pelvic radiotherapy can cause iatrogenic menopause and sudden onset of symptoms such as vasomotor symptoms, mood changes, sleep disturbance and urinary dysfunction.

An individualised approach to managing radiation-induced menopause is recommended depending on age, tumour type, stage, tumour hormone receptor status and presence/absence of uterus [292]. Most vulval cancers are SCCs where systemic and topical HRT are not contraindicated [292–294]. Evidence does not support or contradict the use of HRT in patients treated for vulval melanoma, although is unlikely to be harmful.

Professional resources: Endocrine late effects guidance for healthcare professionals | Macmillan Cancer Support and Fertility and cancer | Macmillan Cancer Support.

**Patient resources: Late effects of pelvic radiotherapy | Macmillan Cancer Support**

*Nervous tissue late effects*

Radiation induced lumbosacral plexopathy (RILP) is an under-reported late effect of pelvic radiotherapy, it is a rare event but potentially increasing with improved survival rates [295,296]. Patients should be informed of the increased risk of neuropathies, such as chemotherapy induced peripheral neuropathy and radiation induced lumbosacral plexopathy. Defining and avoiding the lumbosacral plexus during radiotherapy planning and delivery may reduce doses and late consequences [297,298].

Patients present with bilateral lower limb pain, numbness, weakness, paresis or paralysis [297]. MRI may be useful to rule out recurrence and aid the diagnosis of RILP [299].

Neurological damage is irreversible and there are currently no effective therapies, patients may benefit from supportive care.

## Follow up

*Follow up of VSCC*

There are no clinical trial data to inform the optimum follow up strategy in VSCC and strategies (Table 15) are therefore based on expert opinion [300]). Background vulval dermatoses influence the risk of recurrence and should therefore be taken into account. VSCC arising on a background of dVIN is more likely to recur than on a background of uVIN [66]. 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 to 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 when disease occurred of a background of uVIN was much less (OR 1.35; 95 % CI 0.20 to 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 [92]. However, those with unifocal, HPV-related disease are at lower risk and 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 five years.

Follow up should include clinical examination of the vulva and groins with assessment for physical and psychological sequelae of treatment. Loco-regional recurrence most commonly occurs in the first two years and follow-up regimes should reflect this. 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 [167] (see above). 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 follow-up visit 10–12 weeks post-definitive (chemo)radiation, imaging with MRI scan ± CT/CT-PET is recommended to document response to treatment.

*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.

*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 [132].

*Follow up of vulval malignant melanoma*

See the ano-uro-genital mucosal melanoma guidelines for further information (https://melanomafocus.com) [1].

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

| 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 dVIN/ LSA. | Grade D |
| Those with no recurrence of HPV-dependent VSCC or uVIN could be discharged to patient-initiated follow-up, with access to rapid re-referral after five years. | Grade D |
| Those with recurrent disease, HPV-independent VSCC 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 | |
| Basal cell carcinoma | |
| An initial follow up 3 months following surgery may be appropriate to check healing and local recurrence. In patients without Gorlin's syndrome, 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 |

## Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: JM - None to declare. PB - None to declare. LH - None to declare. AA-None to declare. LB- Works for Perci Health Ltd, 1 Vincent Square, London, SW1P 2PN and director of Buckley Consultants Ltd. KE- Royal College of Obstetricians and Gynaecologists Workforce Fellow Jan 2022-Dec 2022. Paid for 8 h/week via her organisation. CF – Has received payments for participation on a Data Safety Monitoring Board or Advisory Board for Glaxo Smith Klein, Roche, Ethicon, Astra Zeneca MSD (Merck & Co., Inc). RG – Has received payments for lectures from Astra Zeneca, Oncoinvent and MSD. AT - Has received financial support to attend meetings and for participation on a Data Safety Monitoring Board or Advisory Board from MSD.

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## Appendix A. Supplementary data

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