All Wales Guideline for the Management of Vulval Cancer

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The purpose of this document is to provide guidelines for the diagnosis and management of adult patients with vulval carcinoma treated in Wales.

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1 Introduction & Background

Vulval cancer is the 4th most common gynaecological cancer in the UK. It is a rare disease with a crude incidence rate of 3.9/100 000 [6]. In 2015, vulval cancer was less than 1% of all new cancer cases registered that year with 1,300 new cases registered in the UK. In Wales, vulval cancer accounts for 3-5% of all female genital tract cancers (Welsh Cancer Intelligence and Surveillance Unit data).

Incidence in the UK is highest in females over 90 years of age.[6] The incidence of vulval cancer has increased by 18% since the early 1990s with most of it diagnosed in women over 70 years of age. The increase in incidence in younger women is most likely due to an increase in human papilloma virus (HPV)-related VIN (vulval intra-epithelial neoplasia).

Squamous cell carcinomas represent approximately 90% of vulval cancers. The main risk factors for the disease are infection with high risk HPV, lichen sclerosis and lichen planus. HPV16 is the most common viral subtype associated with vulval cancer. The other 10% non squamous type of vulval cancer are primary vulval melanoma, basal cell carcinoma, Bartholin's gland carcinoma, adenocarcinoma, and rarely sarcoma.

In 2014, there were 450 deaths associated with vulval cancer in the UK, which is less than 1% of all cancer- related deaths in females that year. The majority of deaths result in women over 70 years of age as the mortality rate increases with age. The mortality rates in this age group have reduced by 30% since the early 1990s. The effects of HPV vaccination reducing vulval cancer are still unknown and it may take decades to possibly study this effect, however, a decrease in vulval cancer associated with HPV is expected to occur. A decrease in vulval cancers caused by vulval dermatoses (lichen sclerosis and lichen planus) is not expected to occur.

2 Presentation

Most vulval carcinomas present with a specific lesion on the vulva. This lesion may be symptomatic with pain or bleeding associated with the area on the vulva. Clinical features of highly suspicious of vulval cancer include a fungating lesion +/- palpable groin lymph nodes. Some lesions will be found on clinical examination after noticing groin lymph node(s) enlargement.

For presentation of vulval cancer see Table 1 below.

Presenting symptoms	Association
Vulval lesion – asymptomatic.	All types of vulval CA
Vulval lesion- symptomatic; pain or bleeding	All types of vulval CA
Vulval fungating lesion	Highly suspicious of vulval cancer
Palpable groin nodes	Highly suspicious of vulval cancer
Vulval lesion which may or may not be pigmented	Vulval melanoma
Vulval lesion with itching	Vulval melanoma
Asymptomatic lesion which may include an irregularly outlined pigmented or non-pigmented macule, papule, patch or nodule with or without ulceration	Vulval melanoma
Discrete vulval lesion or classical raised, rolled- edge ulcer, without a background dermatosis or evidence of uVIN	Basal cell carcinoma
Painful mass in the vulva/lower vagina over the area of the Bartholin's gland.	Bartholin's gland carcinoma

Table 1

3 Diagnosis

Women with highly suspicious clinical features for vulval cancer could be referred to a cancer centre without the need to wait for a biopsy result; however it is preferable to have confirmation of cancer before referral as this will help guide management. Vulval punch biopsies may not sufficiently sample the lesion particularly if it is large and / or deep.

An incisional biopsy such as a punch or wedge biopsy should include the edge of a lesion, where transition from normal to abnormal tissue is evident. Biopsy should ideally be taken from the area that looks most suspicious/concerning. Avoid taking biopsies from the centre of an ulcer which may not be diagnostic. Biopsies should be taken with sufficient depth to demonstrate differentiation between superficially invasive cancer and those with invasion > 1mm as this will determine subsequent management.

Excision biopsies should be avoided as this may affect options for conservative treatment with wide local excision and sentinel node biopsy. In small lesions, the vulva can heal well and the primary site may be difficult to distinguish at the time of definitive treatment. Exceptions to this may be in frail, elderly patients where it is appropriate to excise a symptomatic, small lesion under local anaesthetic for palliation purposes as well as planning subsequent treatment.

It is recommended that an accurate diagram of the vulva demonstrating each biopsy site be drawn (e.g. https://www.nva.org/what-is- vulvodynia/vulvar-anatomy/).

3.1 Recommendations

- Women with suspicious vulval lesions should be referred to a rapid access clinic for urgent assessment within two weeks of presentation, as per NICE guidelines[7].

- Women highly likely to have vulval cancer on clinical grounds should be referred to a gynaecological cancer centre without waiting for biopsy results, though confirmed cancer referral is ideal.

- 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.

- Suspicious vulval lesions should ideally be sampled with a punch or wedge biopsy from the suspicious area and excisional biopsy avoided until a diagnosis is made.

- Biopsies should include the edge of a lesion to ascertain the background condition.

- A detailed diagram, indicating lesion and biopsy sites, should be drawn.

- Ideally clinical photographs before and after biopsy should be taken, with an indication of scale.

- Biopsies from separate lesions should be sent in separate pots and clearly labelled.

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

Figure 1. Recommendations for presentation and diagnosis

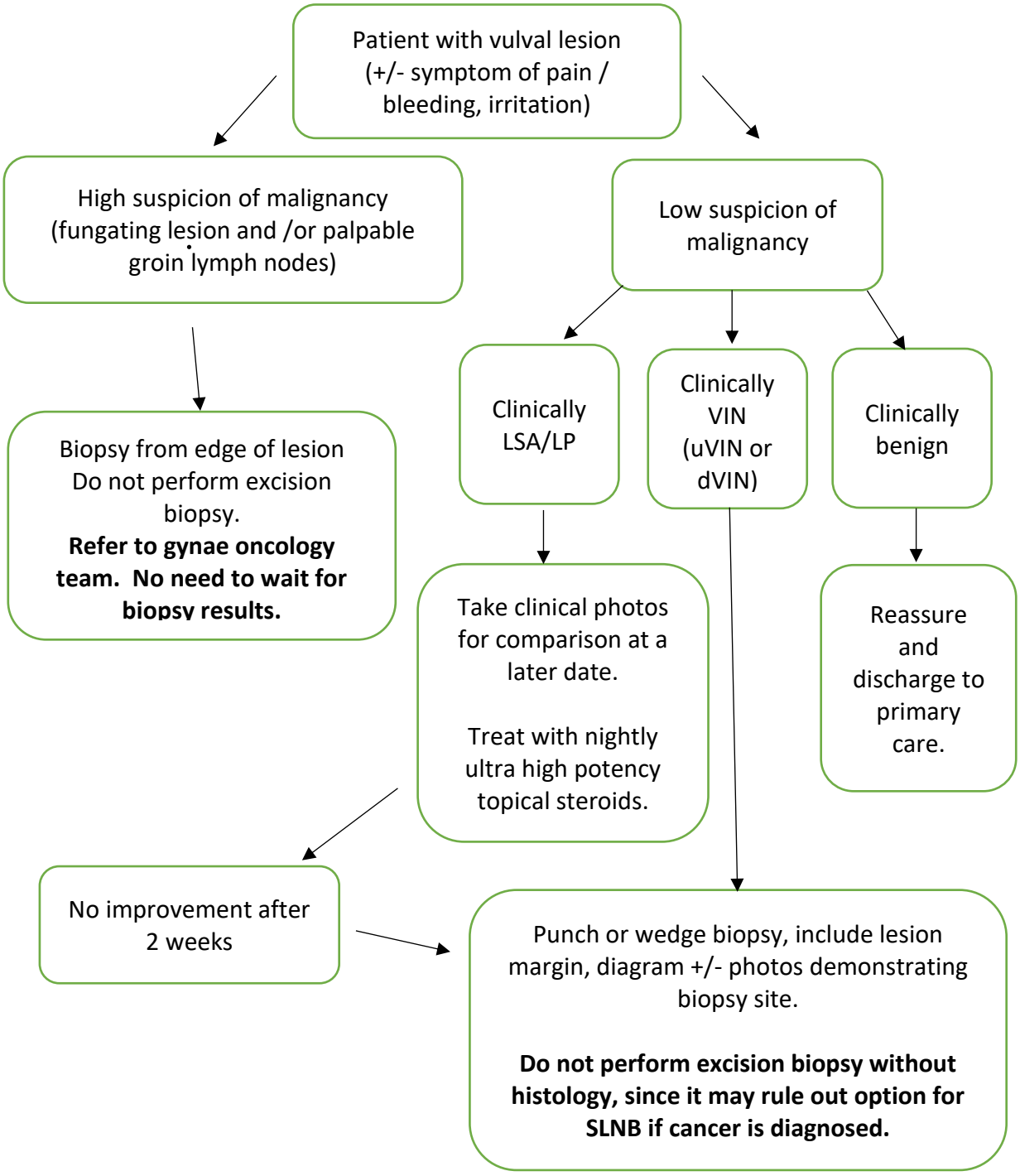

Figure 1. Flowchart exhibiting management of suspicions vulval lesion. LSA= Lichen Sclerosus Atrophicus; LP = Lichen Planus; VIN = vulval intra-epithelial neoplasia; uVIN = usual-type VIN; dVIN = differentiated VIN

4 Screening

There are currently no proven screening tests for vulval carcinoma.

5 Pathology

5.1 Precursor Lesions

For precursor legions see Table 2 below.

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

Table 2

5.2 Squamous Cell Carcinoma (SCC)

SCC is the most common type of vulval cancer constituting 90% of vulval cancers. Invasive SCC may be caused by HPV which is more common in younger patients associated with HPV infection, uVIN and smoking. SCC may also be caused by a p53-related pathogenetic pathway which is more seen in older women associated with dVIN and lichen sclerosus. Verrucous carcinomas are

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

SCC mostly spreads via inguinal lymph nodes. If regional lymph nodes are negative it rarely presents at distant sites from the primary. Groin node biopsy/dissection is recommended for those with greater than FIGO Stage 1a SCC because imaging is poor at excluding microscopic metastases from groin nodes. Clinically evident groin node involvement is a contraindication for performing a sentinel lymph node (SLN) biopsy. Therefore, clinical examination and imaging of the groin is necessary to assess metastatic disease. Ultrasound can be used to assess the groins however it recommended to use cross-sectional imaging such as computer tomography (CT) or magnetic resonance imaging (MRI) of the chest abdomen and pelvis. CT or MRI should be performed before a lymphadenectomy because it may provide information regarding distant disease. Positron emission tomography CT (PET-CT) may be used if radical surgery is being considered.

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 (i.e. they will need groin node dissection and will not be eligible for sentinel lymph node biopsy). Evaluation of the pelvic nodes with cross sectional imaging (MRI or CT) is recommended before undertaking lymphadenectomy.

5.2.1 Lymph node metastasis

The number of lymph nodes involved, the size of the largest metastatic deposit and whether extra nodal spread is present or absent should be recorded. Nodal deposits larger that 5mm in size are correlated with poorer survival.

5.2.2 Sentinel lymph nodes (SLN)

A SLN is a node which collects drainage directly from the primary tumour. Examination of tissue which is paraffin-embedded is recommended. An intraoperative frozen section of lymph nodes could cause tissue loss. All nodal tissue must be sampled. The technique is described in detail in the British Association of Gynaecological Pathologists' document on protocols for processing of sentinel lymph nodes.[2]

Definitions of nodal involvement

The size of the metastases in the lymph node affects the stage allocated.

These are defined as:

Macrometastasis: >2mm pN1;
Micrometastasis: >0.2mm to</=2 mm pN1 mi;
ITC – individual tumour cells – microscopic clusters and single cells </= 0.2 mm pN0(i+).

Extra-nodal involvement

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

5.3 Vulval Paget's disease (VPD) and Invasive adenocarcinoma of the vulva

Paget's disease of the vulva and intra-epithelial adenocarcinoma occur most commonly in postmenopausal white women. Intra-epithelial adenocarcinoma arises most on the vulva. In most cases the pathology is confined to the epithelium, however in up to 20% of cases there is involvement of the underlying stroma. [6] After treatment for non-invasive VPD the risk of progression to invasive disease or metastasis is low.

Lesions of VPD are usually well demarcated, painful, erythematous and are most commonly on the labia majora. Lesions may resemble eczema. The tumour cells express cytokeratin 7, carcinoembryonic antigen and apocrine cell marker GCDFP15, which may help to distinguish VPD from other intra-epidermal neoplasms such as malignant melanoma *in situ*. The borders of the lesions seen clinically correlate poorly with the histological extent of the disease, which may account for the high rate of recurrence after primary surgery.

5.4 Vulval Melanoma

Up to 40% of women present with vulval melanoma as regional or distant metastases. Vulval melanoma as a primary disease is rare compared with ultraviolet light exposed sites. The prognosis for vulval melanoma is relatively poor with a 5-year survival rate of 58% compared to 81% for cutaneous melanoma. [6] Vulval melanoma lesions are usually asymmetric with irregular borders, uneven pigmentation and occasionally ulcerations. Lesions may also be amelanotic in up to 25% of cases. Adverse prognostic factors are advanced clinical stage, Breslow thickness

greater than 1mm, vertical growth phase, ulceration and mitotic index over 1 per mm^2. Microsatellite lesions and perineural invasion are associated with increased local recurrence. [6]

6 Staging

Staging should be performed using the International Federation of Gynaecology and Obstetrics (FIGO) Staging System for Vulval Cancer 2021 which may be seen in Table 3 below:

FIGO staging for carcinoma of the vulva 2021

Stage	Description
I	Tumour confined to the vulva
	IA Tumour size ≤2 cm and stromal invasion ≤1 mm
	IB Tumour size >2 cm or stromal invasion >1 mm
II	Tumour of any size with extension to lower one-third of the urethra, lower one-third of the vagina, lower one-third of the anus with negative nodes
III	Tumour of any size with extension to upper part of adjacent perineal structures, or with any number of nonfixed, nonulcerated lymph node
	IIIA Tumour of any size with disease extension to upper two-thirds of the urethra, upper two-thirds of the vagina, bladder mucosa, rectal mucosa, or regional lymph node metastases ≤5 mm
	IIIB Regional lymph node metastases >5 mm
	IIIC Regional lymph node metastases with extracapsular spread
IV	Tumour of any size fixed to bone, or fixed, ulcerated lymph node metastases, or distant metastases
	IVA Disease fixed to pelvic bone, or fixed or ulcerated regional lymph node metastases
	IVB Distant metastases

Table 3

- Depth of invasion is 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.
- Regional refers to inguinal and femoral lymph nodes.

7 Management of Primary Disease

7.1 Imaging

Once diagnosis of vulval cancer is obtained, imaging is essential to ascertain the extent of disease. Ultrasound can be used to assess the groins however it is recommended to use cross-sectional imaging such as computer tomography (CT) of the chest, abdomen and pelvis to obtain information regarding distant disease.

Gross nodal involvement should be excluded by clinical examination and appropriate imaging / radiologic staging. FNA or core biopsy can be used to evaluate suspicious nodes when this would alter primary treatment, although removal of involved lymph nodes should be considered standard of care. 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. No additional imaging is required in the pre-op assessment of BCC lesions, unless there is a clinical suspicion of nodal disease. 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. The histology and imaging should be discussed in the gynaecological cancer MDT for decision on further management.

7.2 Surgery

7.2.1 Vulval SCC

Treatment of vulval carcinoma is surgery with curative intent for local disease. For FIGO stage IV tumours, radical surgery is inappropriate, however, surgery may be used for palliation of symptoms. Management of vulval cancer should be tailored to the patient based on site and size of the cancer lesion.

Surgery should include radical local excision with separate incisions for the groin lymphadenectomy. This surgical approach is associated with lower morbidity and mortality rates. [3,4] En-bloc resection of the vulva and groin nodes may be considered if there is a large and/or fixed nodes where risk of recurrence in the skin bridge is higher.

Treatment of vulval cancer should be planned pre-operatively ideally with diagrams for the patient to confirm sufficient consent is taken. Patients should be informed about changes that may occur

in sexual function postoperatively, especially if the clitoris and surrounding area is involved. The excision margins should be planned prior to surgery. The tissue should not be stretched during this process and the natural state of the respective tissue should be respected and considered during planning.

The intent of surgery for the primary tumour is removal of the cancer with clearance at all margins also involving the deep margin (at least 2mm clearance margin). Margins should be clear of disease however large negative margins are not required in node-negative patients treated with surgery alone. [8] In case of recurrence, the tumour is more often a new primary tumour within an area of field change as indicated by the presence of lichen sclerosus of VIN at the margins. [6]

Stage 1a Vulval SCC

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 vulval SCC where there may be less tissue available for closure.

Stage 1b Vulval SCC

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

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

plastic surgery team may be required. In some cases, tumour may need to be shrunk with radiotherapy +/- chemotherapy prior to consideration of surgery.

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

Closure may involve primary closure or more complex reconstructive techniques. 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 stage II VSCC, and excision of the distal urethra and vagina should be considered. In cases where the anus is involved concomitant chemoradiotherapy (CCRT) (or neoadjuvant chemoradiotherapy) may be considered to shrink the tumour, thus allowing adequate margins to be attained surgically without compromise of faecal continence. 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 stage III VSCC as for earlier stages with removal of the groin lymph nodes. Recurrence in the skin bridge between the positive lymph node and the primary tumour is low. [(6)]

Stage IV VSCC

Surgery rarely has a role in advanced disease. Palliative procedures may be considered to ease discomfort, which is otherwise difficult to control. In cases of fistulation of the tumour to bowel or bladder, de-functioning stomas and/ or urinary diversions or nephrostomies can be considered.

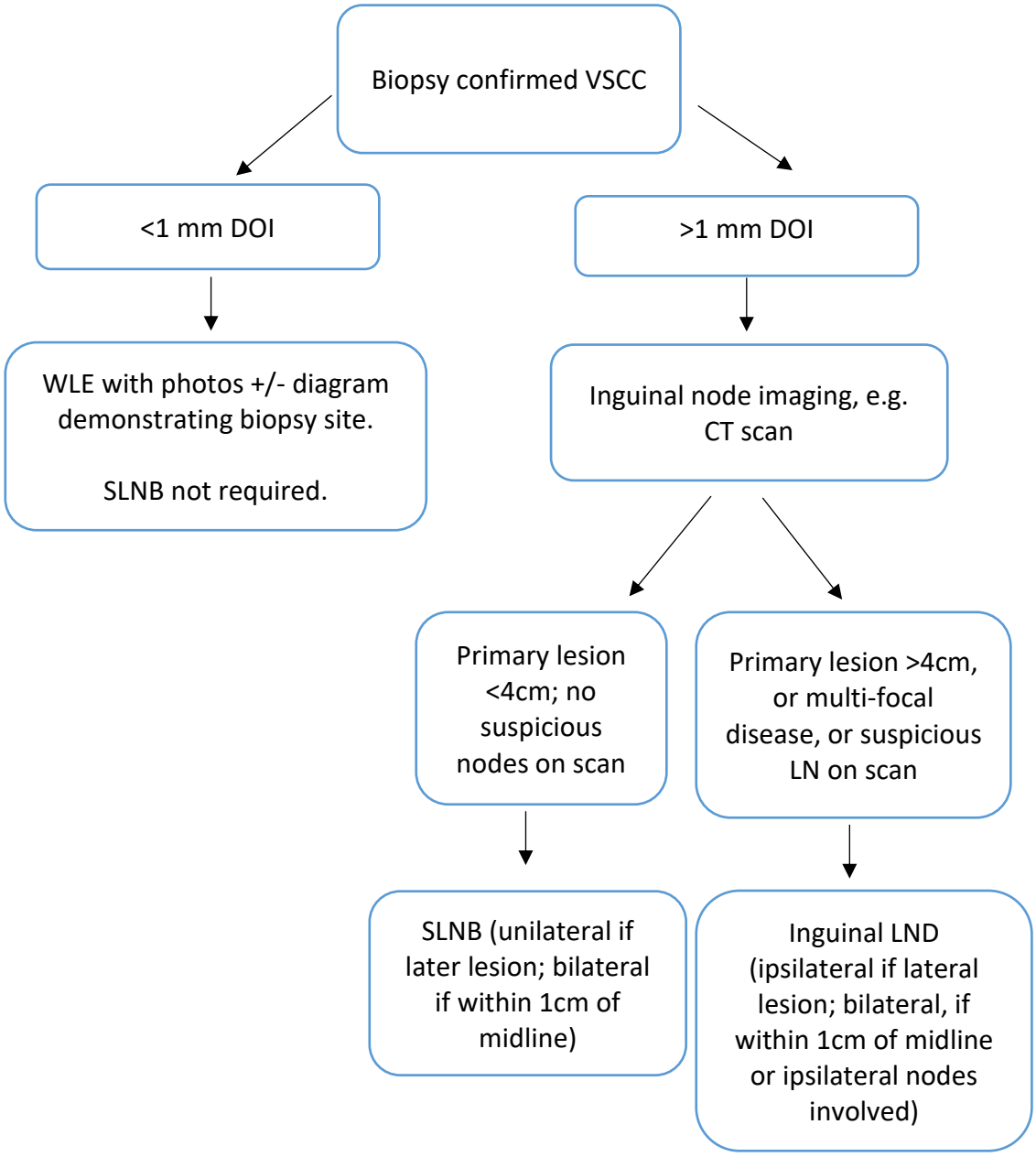

Figure 2. Management of primary lesion. VSCC = vulval squamous cell carcinoma; DOI = depth of invasion; WLE = wide local excision; CT = Computerised tomography scan; SLNB = sentinel lymph node biopsy; LND = lymph node dissection.

Recommendations for surgical treatment of primary site of VSCC

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

7.3 Recommendations for treatment of rare vulval malignancies

7.3.1 Bartholin's Gland Carcinoma

- Patients with Bartholin's gland carcinoma may need multi-modal treatment and full body imaging with CT of thorax, abdomen and pelvis is recommended prior to surgery, as disease is more likely to present at an advanced stage.

7.3.2 Vulval Paget's Disease

- Consider investigations to exclude a co-existing malignancy of the breast, gynaecological, urological and colorectal tracts at diagnosis.
- 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.
- Imiquimod may be of benefit and reduce the need for surgery, if invasive disease is excluded.
- Radiotherapy or photodynamic therapy have been used in VPD, but the certainty of this evidence is very low and should be considered with caution.

7.3.3 Vulval Malignant Melanoma

- Patients should be treated with close collaboration of the gynae-oncology and melanoma MDTs.
- Surgery should aim to achieve an R0 resection (no microscopic disease within <1 mm of margins) with the least radicality.
- Sentinel node dissection may help to guide adjuvant immunotherapy and should be considered after discussion with the Melanoma MDT.
- Metastatic regional nodal disease may be considered for removal as treatment may improve quality of life, but without evidence of survival benefit.

7.4 Recommendations for management of groin nodes

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

7.5 Recommendations for sentinel lymph node dissection

Sentinel node dissection is the procedure of choice for small (<4 cm), unifocal tumours without clinical or radiological evidence of lymph node metastasis at presentation providing representative injection is possible and the tumour does not encroach on the urethra, vagina or anus.

There is a clear learning curve for SLND and the technique should be performed by clinicians/centres with appropriate levels of training and expertise to maintain practice.

The use of radioisotope is mandatory for SLND. Vital or fluorescent dyes may be used in addition to radioactive tracer.

Preoperative lymphoscintigraphy is recommended to enable the identification, location and number of sentinel nodes.

When a sentinel lymph node (SLN) is not found (method failure) inguinofemoral lymphadenectomy should be performed.

For tumours involving the midline, bilateral SLND should be performed. The identification of a unilateral SLN in such tumours should be regarded as ‘method failure’ and inguinofemoral lymphadenectomy of the contralateral groin (no sentinel found) is recommended.

Intra operative assessment of the SLN by frozen section can potentially be used to avoid the need for a second procedure in node positive disease. However, caution is required due to the loss of tissue that arises from this process and the potential risk of a false negative sentinel node.

Pathological assessment of the SLN should include ultra staging when the node is negative on standard H&E sectioning. Ultra staging should include serial step sectioning at least every 200 µm with the use of immunohistochemistry where the H&E sections are negative.

When metastatic disease is identified in the SLN, inguinofemoral lymphadenectomy for the groin affected by metastatic disease is the current treatment of choice.

Evidence does not suggest that sentinel nodes with isolated tumour cells should be treated as positive nodes.

8 Reconstructive Surgery

1. The resecting surgeon should not be tempted to limit their surgical excision by the constraints of soft tissue closure.
2. Before surgery, there will ideally be a combined excision/reconstruction examination, either in clinic or under anaesthesia, to plan which tissues to excise and allow full pre-operative counselling regarding reconstruction.
3. If the anal margin is involved by the disease, the two potential approaches are: temporary or permanent stoma with excision of the required amount of anal margin; or neo-adjuvant (chemo)radiotherapy with the aim of down-sizing the disease & allowing preservation of the anus.
4. If the resection margin will lie within 1 cm of the anal margin, consider faecal diversion, either as a combined procedure or 2 weeks pre-operatively. Usually, margins greater than 1 cm do not require a stoma.
5. Local flap reconstruction is possible after radiotherapy to the flap field, but the length to breadth ratio of the flap may need to be modified to avoid tip necrosis.
6. Skin grafting is also possible after radiotherapy, though graft ‘take’ may be reduced if the wound bed has a poor vascular supply. Local flaps may be quicker to heal than skin grafts in the post-radiotherapy wound bed.
7. If excision margins are difficult to assess, frozen section should be considered before planning flaps for reconstruction.
8. After flap reconstruction, if lateral margins are incomplete then the margin of the flap & an appropriate amount of native tissue can be excised. If the deep margin is involved, a thick flap may be lifted in a more superficial plane and replaced after excision of deeper tissues. However, a thin flap may need to be entirely excised with the underlying soft tissue to obtain a clear margin. For this reason, if there is uncertainty about surgical margins, delayed flap reconstruction with either dressings, direct closure or skin graft while pathology is obtained should be considered.

9 Recommendations for neoadjuvant/adjuvant treatment of advanced disease

9.1 Primary Radiotherapy

Primary radiotherapy should be considered in patients who are deemed inoperable due to the extent of the disease or where the disease involves or is close to the anal sphincter and the patient does not want a colostomy or if the patient is unfit for an anaesthetic. The radiotherapy will be radical or palliative depending on the situation.

Radiation is typically delivered via external beam and Intensity Modulated radiation therapy (IMRT), or Volumetric Modulated Arc Therapy (VMAT) is recommended which allows greater precision of radiotherapy delivery and helps reduce both short and long term toxicity. However, in selected patients a boost may be applied with an interstitial implant.

For definitive treatment the dose required is more than 60Gy which Is usually given over 2 phases. Phase 1 delivers 45-50GY to the pelvis and groins followed by a phase 2 photon or electron boost to gross disease of 15 to 20Gy. With IMRT further integrated boosts may be used.

Concomitant cisplatin at a dose of 40mg/m² weekly should be considered as a radiosensitizer in appropriate patients receiving radical radiotherapy.

In certain situations, primary radiotherapy, with or without chemotherapy, may be given as neoadjuvant with the intent to decrease the size of cancer to make it operable/sphincter saving.

9.2 Adjuvant Radiotherapy

In the post operative setting radiotherapy should be considered if the resection margins are positive and further surgical excision is not possible. It should also be considered in cases of close pathological margins to reduce the frequency of local recurrences. Although there is no consensus for the threshold of pathological margin distance below which adjuvant radiotherapy should be advised margins of <2mm are associated with increased local recurrence rates.

Ideally radiotherapy should be started within 6 weeks of surgery using similar techniques as with primary radiotherapy with IMRT or VMAT.

Adjuvant radiotherapy should be considered when:

- positive excision margins of the primary tumour, and further surgical excision is not possible;
- pathological margins <2 mm, where repeat excision is not recommended or possible, even though no consensus for the threshold of pathological margin distance exists. Each case should be individualised and discussed at MDT, considering patient factors (co-morbidities, previous treatment), location of close margins, and need for groin/pelvic radiotherapy;
- presence of 2 or more positive inguinal lymph nodes or a solitary node with extracapsular spread.

9.3 Palliative Radiotherapy

This should be considered in situations where the patient is not suitable for radical treatment either due to fitness or where other treatment options are not acceptable or clinically appropriate. It may be used for alleviating symptoms such as pain, ulceration or bleeding. Short fractionation schedules should be used to reduce toxicity such as 20Gy in 5 fractions or 30Gy in 10 fractions. A single fraction of 8 or 10 Gy is sometimes appropriate which can be repeated if appropriate.

9.4 Chemotherapy

9.4.1 Neoadjuvant setting

This is considered in the following patients:

1) Too unwell for radical curative surgical or radiotherapy treatment
2) Have large volume of primary/nodal disease who could have more conservative treatment if down staged.

9.4.2 Adjuvant setting

Adjuvant chemotherapy is not normally given alone and is normally given concomitantly with radiation treatment.

9.4.3 Palliative setting

Palliative chemotherapy should be considered in patients with metastatic disease or where no further options of radiotherapy or surgery are available. Treatment is given with the intention of palliating symptoms to try and improve quality of life. There is no standard treatment and no preferred regimens from the literature so clinical trials should be considered. In patients who are fit combination chemotherapy with regimens such as cisplatin and capecitabine/5-fluorouracil, carboplatin and paclitaxel, and mitomycin c and 5 fluorouracil/capecitabine may be offered. PD1 and PDL1 inhibitors have shown significant activity in squamous cancers of other sites and these are currently being trialed in vulval cancer. Other immunotherapy approaches such as vaccines and tumour infiltrating lymphocytes (TILs) may also have an important role in addition to anti-viral therapy.

10 Treatment of recurrent disease

Management of recurrent disease may be challenging and should be undertaken via 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 patient will require re-staging and the patient's wishes should be taken into consideration as well since it may determine whether radical or palliative approach would be more appropriate.

10.1 Possible options for treatment

- Further surgery
- Radical radiation therapy with or without chemotherapy
- Interstitial implant in small local recurrence
- Neoadjuvant chemotherapy followed by tailored therapy
- Consideration of a clinical trial
- Palliative radiotherapy
- Palliative chemotherapy
- Novel approaches including immunotherapy
- Best supportive care

10.2 Recommendations for treatment of recurrent disease

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

11 Long term complications of treatment

11.1 Lymphoedema

Lymphoedema of the legs may present from 16.7-49.2% of patients after lymph node dissection. It may be significantly worse in patients who have had both surgical treatment as well as radiotherapy. [(6)] Those women who develop lymphoedema should be referred to a specialist lymphoedema service for management. Lympho-vascular anastomosis surgery may be an option for those with severe symptoms, especially in the presence of recurrent cellulitis, although availability of this service is limited.

11.2 Bladder & Bowel Function

At every follow up, questions should be asked regarding any new problems relating to bowel/bladder function. If present, initially manage with simple solutions such as loperamide for diarrhoea, dietary changes for constipation, anticholinergics for bladder urgency.

Consider referral to other services for persistent problems that are affecting quality of life e.g. gastroenterology, colorectal, urodynamic, continence or urology, as appropriate.

A recent Cochrane review found that conformational RT methods help to reduce radiotherapy-related side effects. There was a scarcity of evidence to robustly support the use of any single drug or non-drug option to reduce radiotherapy-related effects on bowel function. They concluded that more high-quality research was required to help inform patients and clinicians how best to manage common pelvic radiotherapy-related side effects.

11.3 Psychological/psychosexual support

Psychosocial and psychosexual support should be provided throughout the entirety of the patient's pathway and included in all stages of counselling and treatment.

- Specialised psychosexual counselling services should be available to all women with a diagnosis of vulval cancer.
- All patients should be informed of predictable short- and long-term effects of treatment during the consent process.
- Patients should receive written information about the disease and management of side effects at appropriate stages of the treatment pathway.
- All patients should be offered an HNA at key stages of the cancer pathway as part of the Recovery Package to support patients living with and beyond cancer.
- Referral to other specialist to manage symptoms that affect quality of life should be considered. Women should have the opportunity to explore ways of improving their quality of life through appropriate support and signposting to survivorship/living with and beyond cancer, and psychological services where available.

The following information from Macmillan may be used to support patients:

https://www.macmillan.org.uk/information-and-support/vulva-cancer

https://be.macmillan.org.uk/be/s-605-radiotherapy.aspx

https://www.macmillan.org.uk/cancer-information-and-support/after-treatment

https://www.macmillan.org.uk/cancer-information-and-support/impacts-of-cancer/lymphoedema

11.4 Sexual Morbidity

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

12 Follow up of Vulval carcinomas

12.1 VSCC

- There is no proven regimen for follow up of VSCC. However, recurrence rates/new foci are common, especially on a background of LSA.
- Follow up should include clinical examination of the vulva and groins with assessment for physical, psychological, and psycho-sexual effects of treatment.
- The All Wales Guideline for vulval cancer follow up recommends[5].
    - three-monthly follow up for year 1 and 2
    - annual follow up in years 3, 4 and 5 years
- Those with recurrent disease and multi-focal disease will need life-long follow up.
- Those with no recurrence of VSCC or uVIN could be discharged with access to rapid re-referral after 5 years.
- All patients should be told to report new lesions and be seen urgently since interval cancers are not uncommon and should be treated promptly.

12.2 Vulval Malignant Melanoma

- All Wales Guideline for gynaecological cancer follow up suggests:
    - three-monthly follow up for year 1 and 2
    - six monthly follow up for year 3
    - annual follow up in years 4 and 5 years

12.3 Basal Cell Carcinoma

An initial follow up 3 months following surgery may be appropriate to check healing and local recurrence. Further follow up is not required, if completely excised.

12.4 Vulval Paget's Disease

Patients with Vulval Paget's Disease should have long-term follow-up. The follow up regimen recommended for the VPD is:

- three-monthly follow up for year 1 and 2
- annual follow up life long

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 gynaecological cancer clinic is suggested.[9]

13 References

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3. Gunther V, Malchow B, Schubert M, et al. Impact of radical operative treatment on the quality of life in women with vulvar cancer--a retrospective study. Eur J Surg Oncol. 2014;40(7):875-82.

4. Hacker NF, Leuchter RS, Berek JS, Castaldo TW, Lagasse LD. Radical vulvectomy and bilateral inguinal lymphadenectomy through separate groin incisions. Obstet Gynecol. 1981;58(5):574-9.

5. Leeson S. All Wales Guideline for Gynaecological Cancer Follow-up. Wales Cancer Network. Version 2. Published date: 19 February 2021.

6. Morrison J, Baldwin P, Buckley L, et al. British Gynaecological Cancer society (BGCS) Vulval Cancer Guidelines: Recommendation for Practice. Published date: 15 May 2020.

7. National Institute for Health and Care Excellence. Suspected cancer: recognition and referral. NICE guideline [NG12]. National Collaborating Centre for Cancer; 2017 Published date: 23 June 2015; Last updated: 15 December 2021.

8. Royal College of Obstetricians and Gynaecologists. Guidelines for the Diagnosis and Management of Vulval Carcinoma. London: RCOG; 2014.

9. Woelber L, Griebel L-F, Eulenburg C, et al. Role of tumour-free margin distance for loco-regional control in vulvar cancer—a subset analysis of the Arbeitsgemeinschaft Gynäkologische Onkologie CaRE-1 multicenter study. European Journal of Cancer. 2016;69:180-8.

13.1 Useful Resources

https://executive.nhs.wales/networks/wales-cancer-network/clinical-hub/cancer-site-groups/gynaecological-cancer/