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# Cancer of the vulva

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## Abstract

Vulvar cancer is an uncommon gynecological malignancy primarily affecting postmenopausal women. There is no specific screening and the most effective strategy to reduce vulvar cancer incidence is the opportune treatment of predisposing and preneoplastic lesions associated with its development. While vulvar cancer may be asymptomatic, most women present with vulvar pruritus or pain, or have noticed a lump or ulcer. Therefore, any suspicious vulvar lesion should be biopsied to exclude invasion. Once established, the most common subtype is squamous cell carcinoma. Treatment of vulvar cancer depends primarily on histology and surgical staging. Treatment is predominantly surgical, particularly for squamous cell carcinoma, although concurrent chemoradiation is an effective alternative, particularly for advanced tumors. Management should be individualized, and carried out by a multidisciplinary team in a cancer center experienced in the treatment of these tumors.

KEYWORDS

Cancer staging; Chemotherapy; Diagnostic imaging; FIGO Cancer Report; Radiotherapy; Risk factors; Surgery; Therapy; Vulvar cancer; Vulvar neoplasms

## 1 | INTRODUCTION

Vulvar cancer is uncommon, accounting for only 2%–5% of gynecologic malignancies. Squamous cell carcinoma (SCC) of the vulva, the most common subtype, has traditionally been regarded as a disease of postmenopausal women, although the mean age of incidence has fallen in recent years owing to the increase in HPV infections worldwide.[1,2] Reinforcing this epidemiological change, differences in terms of current incidence or age at presentation can be found between countries and regions; some may be explained by a different local HPV prevalence or other risk factors (e.g. ethnic distribution, smoking, atrophy or inflammation, HIV).[3–6]

## 2 | ANATOMY

The external genitalia comprise the vulva and the mons pubis or pubic area. The vulva is located in the anterior triangle of the perineum. The elements that make up the vulva include the labia minora and major, clitoris, bulb of the vaginal vestibule, and the lesser (Skene glands) and greater (Bartholin glands) vestibular glands.[7] Most malignancies are associated with the skin of the labia. Malignancies arising from the clitoris and vestibular glands are extremely rare.

Lymphatic drainage from the vulva is primarily to the inguinofemoral region, and secondarily to the external and internal iliac region. This drainage is shared with the inferior third of the vaginal tube and the most external portion of the anus (below the anal sphincter). Depending on the localization of the primary tumor, its size, and its closeness to the midline, lymphatic drainage can be unilateral or bilateral. Additionally, if the lesion is close to or on the clitoris, drainage can be directly to the iliac region.[8]

## 3 | PREVENTION

### 3.1 | Primary prevention (vaccination)

As for cervical premalignant lesions predisposing to cervical cancer, persistent HPV infection, particularly by HPV 16 subtype, has been associated with the long-term development of high-grade squamous

intraepithelial lesion (HSIL) and SCC of the vulva.[9–11] The introduction of HPV vaccination as a primary prevention strategy in cervical cancer has been shown to also reduce the prevalence of noncervical premalignant lesions among vaccinated women.[12] Long-term trends analyses by the Norwegian Cancer Register also show promising estimates of reduction in HPV-associated cases of vulvar cancer in future years, among HPV-vaccinated communities.[13]

### 3.2 | Secondary prevention (screening)

There is no evidence for specific screening for vulvar cancer. Self-examination in women with lichen sclerosus, a condition related to vulvar cancer development, should be encouraged.[14] In addition, there should be early evaluation of any patient with signs (e.g. pigmented lesions, irregular ulcers) or symptoms (e.g. chronic vulvar pruritus) commonly associated with vulvar disease, who could be a candidate for skin biopsy.[15]

Finally, women who are known to have squamous intraepithelial lesion (SIL) of the cervix, vagina, or anus should have inspection of the vulva as part of their follow-up colposcopy visits.[16]

### 3.3 | Tertiary prevention (management of premalignant lesions)

An effective strategy to reduce vulvar cancer incidence is the opportune treatment of predisposing and preneoplastic lesions associated with vulvar cancer development.

There are two main pathological pathways that lead to vulvar SCC[17]:

1. Keratinizing SCC usually occurs in older women and is often associated with lichen sclerosus and/or differentiated vulvar intraepithelial neoplasia (dVIN).
2. Warty/basaloid SCC generally occurs in younger women, is caused by persistent infection with oncogenic strains of HPV (particularly HPV 16, 18, 31 and 33), and has SIL as its precursor lesion.[6,18] Lesions are frequently multifocal, and may be associated with SIL in other parts of the lower genital tract (e.g. cervix, vagina, anus). HIV infection and cigarette smoking are also common predisposing factors.[1,3,9,19]

As shown in Table 1, the terminology and definitions for premalignant or precursor lesions of vulvar cancer have been reviewed and changed in the last decades. Currently, such lesions arising from the vulva and the anus are all included and named as "lower anogenital squamous intraepithelial lesions." Under this classification, three subtypes are distinguished for the vulva: low-grade squamous intraepithelial lesions (LSIL); high-grade squamous intraepithelial lesions (HSIL); and differentiated variant. Such distinction correlates with the risk of developing cancer over time.[20–22]

To date, there is no definitive treatment for conditions such as lichen sclerosus. Cornerstone measures include avoiding exposure to precipitating factors (e.g. trauma by local irritants, occlusive moist environment) and the use of potent and ultrapotent topical corticosteroids. Alternative options include the use of topical calcineurin inhibitors (e.g. tacrolimus) or retinoids and photodynamic therapy for selected cases and/or cases resistant to corticosteroid therapy. In women, surgery is restricted to scarring processes leading to functional impairment.[23]

**TABLE 1** Vulvar intraepithelial neoplasia (VIN) terminology changes.

| ISSVD 1986 | ISSVD 2004 | LAST (Lower Anogenital Squamous Terminology) 2012 |
|---|---|---|
| VIN 1 | Flat condylomata or HPV effect | LSIL |
| VIN 2 and VIN 3 | VIN, usual type:<br>1. VIN, warty type<br>2. VIN, basaloid type<br>3. VIN, mixed | HSIL |
| Differentiated VIN | VIN, differentiated type | Differentiated VIN (dVIN) |

Source: Hoang et al.,[20] Bornstein et al.,[21] Sideri et al.[22]

dVIN represents less than 5% of preneoplastic lesions of the vulva. However, it is characterized by a higher rate of progression to squamous vulvar carcinoma, shorter time interval to progression, and higher recurrence rate than HSIL. It is rarely associated with persistent HPV infection (less than 2%). Excision (with 0.5–1 cm margins) constitutes the treatment of choice, to allow proper evaluation and exclusion of occult invasion.[24,25]

Multiple treatment modalities exist for the management of HSIL, but simple excision with 5-mm margins and 4-mm depth is the most common. Excision has the advantage of excluding invasion histologically, but the lack of preservation of vulvar skin results in psychosexual morbidity, particularly in younger women. An alternative option to preserve anatomy is the carbon dioxide laser, but this lacks the assessment of occult invasion. A less destructive option is the use of imiquimod 5% to avoid scarring and sexual dysfunction, particularly in smaller lesions. Moderate quality evidence shows that response rates with imiquimod and cidofovir, another topical treatment, are similar at 6 months compared with surgical management or laser vaporization.[26] There is very little evidence of the effectiveness of topical treatment for HSIL among immunocompromised women.[26] Independent of chosen treatment and margin status, there is risk of recurrence (up to 30%–40%). Therefore, a close follow-up is recommended for at least 2–3 years.[24]

## 4 | MANAGEMENT OF VULVAR CANCER

### 4.1 | Anatomy of disease spread

#### 4.1.1 | Primary site

Malignant tumors of the vulva should be histologically confirmed, and are classified as such when the primary site of origin of the tumor is the vulva. This includes tumors that involve both the vulva and vagina, but excludes secondary tumors from genital and extragenital sites.[27]

### 4.1.2 | Lymph nodes

Inguinal and femoral nodes are the first sites of spread, followed by the pelvic nodes. Depending on tumor size and its localization (closer to the middle line or to the clitoris), the risk of nodal involvement can be unilateral or bilateral.

### 4.1.3 | Metastatic sites

Women who have pelvic lymph node metastases or extrapelvic spread are considered to have Stage IV disease.

## 4.2 | Surgical staging

Vulvar cancer has been surgically staged since 1988 and final diagnosis is based on histological evaluation of the vulvar and lymph node specimens.[19,27,28] The FIGO staging of vulvar carcinoma was revisited and last changed in 2009 by the FIGO Committee on Gynecologic Oncology (Table 2).[16] This system is applicable for most of the malignancies rising from the vulva, except melanoma.

## 4.3 | Histopathological types

Squamous cell carcinomas (SCC) account for the vast majority of vulvar cancers (more than 80%), and melanomas are the next most common cancer. Rarer histological types include:

1. Basal cell carcinoma
2. Verrucous carcinoma
3. Paget's disease of the vulva
4. Adenocarcinoma, not otherwise specified
5. Bartholin gland carcinoma

## 4.4 | Histological grades

1. GX: Grade cannot be assessed
2. G1: Well differentiated
3. G2: Moderately differentiated
4. G3: Poorly or undifferentiated

## 4.5 | Treatment

The treatment of vulvar cancer depends primarily on histology and staging. Other variables influencing management are age, coexistence of comorbidities, and performance status of the patient. Treatment is predominantly surgical, particularly for SCC, although concurrent chemoradiation is an effective alternative, particularly for advanced tumors, and those where exenteration would be necessary to achieve adequate surgical margins.[29] Management should be individualized, and carried out by a multidisciplinary team in a cancer center experienced in the treatment of these tumors.[27,28,30] Other therapies such as chemotherapy and immunotherapies are usually reserved for metastatic or palliative settings, or for the treatment of rare histologies such as melanoma.[28,30–34]

# 5 | MANAGEMENT OF SQUAMOUS CELL CARCINOMA

## 5.1 | Presenting symptoms

While vulvar cancer may be asymptomatic, most women present with vulvar pruritus or pain, or have noticed a lump or ulcer. They may

**TABLE 2** FIGO staging of carcinoma of the vulva.[16]

| FIGO stage | Description |
|---|---|
| I | Tumor confined to the vulva |
| IA | Lesions ≤2 cm in size, confined to the vulva or perineum and with stromal invasion ≤1.0 mm[a], no nodal metastasis |
| IB | Lesions >2 cm in size or with stromal invasion >1.0 mm[a], confined to the vulva or perineum, with negative nodes |
| II | Tumor of any size with extension to adjacent perineal structures (lower third of urethra, lower third of vagina, anus) with negative nodes |
| III | Tumor of any size with or without extension to adjacent perineal structures (lower third of urethra, lower third of vagina, anus) with positive inguinofemoral nodes |
| IIIA | 1. With 1 lymph node metastasis (≥5 mm), or<br>2. With 1–2 lymph node metastasis(es) (<5 mm) |
| IIIB | 1. With 2 or more lymph node metastases (≥5 mm), or<br>2. With 3 or more lymph node metastases (<5 mm) |
| IIIC | With positive nodes with extracapsular spread |
| IV | Tumor invades other regional (upper 2/3 urethra, upper 2/3 vagina), or distant structures |
| IVA | Tumor invades any of the following:<br>1. upper urethral and/or vaginal mucosa, bladder mucosa, rectal mucosa, or fixed to pelvic bone, or<br>2. fixed or ulcerated inguinofemoral lymph nodes |
| IVB | Any distant metastasis including pelvic lymph nodes |

[a]The depth of invasion is defined as the measurement of the tumor from the epithelial–stromal junction of the adjacent most superficial dermal papilla to the deepest point of invasion.

also have abnormal bleeding or discharge, and many will have a history of vulvar symptoms due to underlying lichen sclerosus or HSIL. Advanced vulvar cancer may present with a lump in the groin due to lymph node metastases.[16]

### 5.2 | Diagnosis

Any suspicious vulvar lesion should be biopsied to exclude invasion. This can be done under local anesthetic with a 3 or 4 mm Keyes biopsy instrument, or with an incisional or wedge biopsy. Even if the lesion is small, it is better not to excise the entire lesion at the time of biopsy, as this makes the subsequent definitive surgery difficult to plan.[16]

If the diameter of the lesion is 2 cm or less, and the depth of stromal invasion is less than or equal to 1 mm on the initial biopsy, it is usual to do a radical wide local excision of the lesion to assess the maximum depth of invasion. If no part of the lesion has a depth of invasion greater than 1 mm, then this excision is adequate definitive treatment.[35,36]

### 5.3 | Investigations

1. Cervical cytology, and colposcopy of the cervix and vagina, if applicable, due to the association of HPV-related cancers with other squamous intraepithelial lesions.
2. Full blood count, biochemical profile, liver profile, and HIV testing.
3. Chest X-ray.
4. CT or MRI scan of the pelvis and groins may be helpful, especially for locally advanced tumors, to detect any enlarged lymph nodes in the groins or pelvis, erosion into underlying bone, or other metastases.[37] In addition, CT or MRI could be useful in further treatment planning.
5. $^{18}$F fluorodeoxyglucose ($^{18}$F-FDG) positron emission tomography with computed tomography (PET-CT) can more effectively assess and detect inguinofemoral lymph node involvement compared with CT, influencing the planning of primary surgery and inguinal lymph node dissection to determine the optimum surgical extent without sentinel lymph node dissection and use of frozen sections.[37–39] Additionally, PET-CT might be used with larger tumors when metastatic disease is suspected or in the recurrence scenario.[28]

## 6 | SURGICAL MANAGEMENT OF VULVAR SQUAMOUS CELL CARCIMOMA

Surgical management of vulvar cancer should be individualized, and the most conservative operation that will result in cure of the disease should be performed.[35,36]

More importantly, when treatment options are considered, the most appropriate treatment of: (1) the primary lesion; and (2) the groin lymph nodes, should be considered independently of each other, to maximize the chance of cure, while minimizing treatment-related morbidity.[27,28,30,32,35,36]

### 6.1 | Microinvasive vulvar cancer (Stage IA)

Stage IA vulvar carcinoma is defined as a lesion measuring 2 cm or less in diameter, with a depth of invasion of 1.0 mm or less. The depth of invasion is measured from the epithelial–stromal junction of the most adjacent superficial dermal papilla to the deepest point of invasion.[27] These lesions should be managed with radical wide local excision, and groin node dissection is not necessary.[35]

### 6.2 | Early vulvar cancer

Early vulvar cancers are those confined to the vulva, and where there are no suspicious lymph nodes, either on clinical examination, or with ultrasound or other radiological assessment.[19,27]

The gold standard of treatment for early vulvar cancers is radical wide local excision of the tumor. This is as effective as a radical vulvectomy in preventing local recurrence, but substantially decreases the psychosexual morbidity of the treatment.[40–42] Associated preinvasive disease should also be excised to exclude any other areas of invasion, and to prevent new tumors arising in the so-called "abnormal field." While the surgeon should aim for surgical margins of 2 cm to achieve pathological margins of at least 8 mm (allowing for shrinkage of the fixed tissue), it is now recognized that many "recurrent" vulvar cancers are probably new tumors that have developed in the surrounding abnormal tissue, rather than recurrences due to inadequate margins.[43] The deep margin of the excision should be the inferior fascia of the urogenital diaphragm and, if necessary, the distal 1 cm of the urethra can be removed to achieve an adequate margin, without compromising urinary continence.[27,35]

The appropriate management of the groin lymph nodes is the most important factor in reducing mortality from early vulvar cancer, as recurrences in the groin are associated with poorer survival despite using multimodal therapies as "rescue" treatments.[44] The current standard involves resection of the primary tumor and lymph nodes through separate incisions.[28] This approach allows better healing compared with en bloc resection of the vulva and groins.[45] Both inguinal and femoral nodes should be removed, as inguinal node dissection alone is associated with a higher incidence of groin recurrence.[46] While some reviews have suggested that radiation alone can control microscopic groin disease,[47,48] a small randomized trial suggested that groin dissection, with postoperative irradiation for patients with positive nodes, is superior to groin irradiation.[49]

All women who have Stage IB or Stage II cancers should have an inguinofemoral lymphadenectomy.

Less than 1% of patients who have small lateral lesions (less than 4 cm and ≥2 cm from the vulvar midline) and negative ipsilateral nodes have metastases in the contralateral groin nodes, and therefore an ipsilateral groin dissection is adequate treatment for these patients.[28,35]

Patients who have tumors closer to (<2 cm) or crossing the midline, especially those involving the anterior labia minora, and those women who have very large lateral tumors (>4 cm), or positive ipsilateral nodes, should have a bilateral groin node dissection.[50]

Since the findings of the GROINSS-V study—a European multicenter observational study on the sentinel lymph node procedure

in vulvar cancer—were published, the sentinel lymph node is being utilized increasingly in the management of women with early vulvar cancer. The aim of the procedure is to detect nodal metastases in the "sentinel" node (which primarily drains the tumor), and then to omit a full lymphadenectomy in sentinel node negative patients, thereby decreasing the morbidity associated with a complete inguinofemoral node dissection.[8,51]

Indications for a sentinel node procedure, as per the GROINSS-V study,[51] are:

1. Unifocal tumors confined to the vulva
2. Tumors less than 4 cm in diameter
3. Stromal invasion more than 1 mm
4. Clinically negative groin nodes

Sentinel lymph nodes are identified using both radio-labelled technetium and blue dye.[51,52]

In the GROINSS-V study, 403 women were included and groin recurrences occurred in 2.3% of patients, with a median follow-up of 35 months. Disease-specific survival was 97% after 3 years, and surgical morbidity was substantially reduced.[51]

Of note, when an ipsilateral sentinel lymph node is not detected, a complete ipsilateral inguinofemoral lymphadenectomy must be done. In addition, if an ipsilateral sentinel lymph node is positive, a complete bilateral inguinofemoral lymphadenectomy is recommended.[28,53]

A particular scenario in early disease is in the management of patients with positive groin nodes. The Gynecologic Oncology Group protocol #37 showed that patients who were found to have more than one or grossly positive nodes at inguinal lymph node dissection, had improved outcomes if they had adjuvant pelvic and inguinal radiation compared with those who had pelvic node dissection.[54,55] A more recent study, AGO-CaRT-1, also reported that women with positive groin nodes who received adjuvant radiotherapy directed at the groins had improved survival.[56]

Several studies have demonstrated the prognostic importance of the number and size of groin node metastases, as well as the presence of extracapsular spread.[57–59] Patients with one small lymph node metastasis appear to have a good prognosis after inguinofemoral lymphadenectomy alone, unless extracapsular spread is present, and these women do not appear to benefit from adjuvant radiation.[58–60] Therefore, indications for pelvic and groin irradiation in patients with positive groin nodes are:

1. Presence of extracapsular spread.
2. Two or more positive groin nodes.[27]

All patients who have a positive sentinel lymph node (one or more positive nodes), besides undergoing a full inguinofemoral lymph node dissection, should receive radiotherapy to the groins and pelvis if indicated. The sequel to the GROINSS-V trial, GROINSS-V II, is investigating the efficacy of groin radiation without inguinofemoral lymphadenectomy for patients with a single positive sentinel lymph node 2 mm or less in diameter.[27,28]

In terms of radiotherapy, radiation fields during external beam radiotherapy (EBRT) should include the inguinofemoral and external and internal iliac lymph nodes in most patients. If there are many or bulky positive inguinal nodes, or if pelvic node metastases are suspected, the upper border of the radiation field might be extended.[61] Sometimes, brachytherapy can be added as a boost to anatomically amenable primary tumors.

There is a variety of radiation techniques from which to choose, depending on the patient's body size and shape, and the extent of the disease (e.g. 3D conformal/Anterior–Posterior/Posterior–Anterior [AP/PA] fields, intensity-modulated radiation therapy [IMRT]). To ensure adequate tumor coverage, clinical examination, imaging findings (CT or MRI), and nodal size should be considered to properly define the target volume during 3D planning.[28,61]

Combined photon and electron techniques are frequently used to treat the regional nodes, without overdosing the femoral heads. It is important to adequately include both the superficial and deep inguinal lymph nodes. Under-dosage of superficial inguinal nodes by high-energy photon beams is a risk in thin patients, and care should be taken to avoid this. Enough energy must be used to cover the femoral nodes, if electron beams are used.[27]

IMRT or other inverse-planned, computer-controlled radiation-delivery techniques are more modern methods that have been used in recent years to treat vulvar cancer. The benefits of this are decreased acute radiation adverse effects in skin and soft tissue, but as the treatment planning and delivery of IMRT are complex, and the risk of under-dosage of the target is substantial, these techniques are best utilized by clinicians who have the necessary expertise.[27,28]

Radiation dose is determined by the initial extent of disease, and any known residual. After a groin lymphadenectomy where microscopic inguinal metastases are found, 50 Gy in 1.8–2.0 Gy fractions is usually sufficient. In the case of multiple positive nodes or extracapsular spread, radiation doses up to 60 Gy can be given to a reduced volume. Gross residual disease usually requires 60–70 Gy to achieve a high likelihood of regional disease control.[27,28,61]

A 2015 analysis of the National Cancer Data Base (NCDB) suggested that women with node-positive vulvar cancer benefitted the most from the addition of chemotherapy to radiation.[62]

### 6.3. | Advanced vulvar cancer

Advanced vulvar cancer includes tumors that extend beyond the vulva, and/or where there are bulky positive groin nodes.[27] The management of women with advanced vulvar cancer is complex, and should be individualized and carried out by a multidisciplinary team.

When confronted with advanced vulvar cancer, ideally the status of the groin nodes should be determined before treatment is planned.[27,28,30,32] Patients with clinically suspicious nodes should have fine needle aspiration (FNA) or biopsy of their nodes, and pelvic CT, MRI, or PET-CT may be helpful in determining the extent of inguinal and pelvic lymphadenopathies and the presence of distant metastatic disease.[63]

If there are no suspicious nodes either clinically or on imaging, bilateral inguinofemoral lymphadenectomy may be performed, and if

the nodes are negative, radiotherapy to the groins and pelvic nodes will not be necessary. However, if histology reveals positive nodes, then adjuvant radiation to the groin and pelvis should be offered as for early stage disease.[61]

In cases where surgery is thought to be inappropriate for the individual patient, primary chemoradiation may be used to treat the primary tumor as well as the groin and pelvic nodes.[28,47,48,61]

In patients who have clinically positive nodes, enlarged groin and pelvic nodes should be removed if possible, and the patient given postoperative groin and pelvic radiation.[64] Full lymphadenectomy should not be performed because a full groin dissection followed by groin irradiation may result in severe lymphedema.

Ulcerated or fixed groin lymph nodes should be biopsied to confirm the diagnosis, and then treated with primary radiation, with or without chemotherapy. If there is an incomplete response to radiation, the nodes may then be resected if appropriate.[65]

In terms of the management of the primary tumor, surgical excision of the primary tumor with clear surgical margins and without sphincter damage, whenever possible, constitutes the optimum way to treat advanced vulvar cancer, as well as to palliate symptoms such as local pain and offensive discharge.[35]

If adequate excision of the primary tumor can only be achieved by exenteration and the formation of a bowel or urinary stoma, radiotherapy (with or without concurrent chemotherapy) may be a preferred treatment alternative. Survival is improved if any postradiation residual tumor is resected.[66,67]

Concurrent chemoradiation is a well-described treatment alternative for those patients with large tumors in whom primary surgical resection would damage central structures (anus, urethra), and long-term complete responses have been reported.[68–72] The groin nodes and pelvis may need to be included in the radiation field depending on the status of the groin nodes, as determined initially.[27,28,61]

Neoadjuvant treatment with cisplatin and 5-fluorouracil, or other chemotherapy combinations, has been reported to be effective for preservation of the anal sphincter and/or urethra in patients with advanced vulvar cancer.[73,74] This is the subject of ongoing clinical research.

In relation to radiotherapy planning in advanced vulvar cancer, if the groin nodes are positive and meet the previously described indications for adjuvant radiation, the radiation treatment fields should include the pelvis, inguinal nodes, and vulva. These should be treated to a total dose of at least 50 Gy, with attention to adequate coverage of the inguinal nodes.[27,61]

Gross disease or high-risk areas may be boosted either with appositional fields of electrons selected to provide an adequate dose to the surface and at depth, or with conformal external beam therapy. Large vulvar tumors probably require 60–70 Gy to achieve local control, although the relationship between dose and local control remains the subject of ongoing investigation.[27,61]

### 6.4 | Close surgical margins

Most vulvar cancer recurrences occur on the vulva. It is thought that surgeons should aim for tumor-free pathological margins of 8 mm or more to minimize local disease recurrence. Multiple retrospective studies have tried to assess the factors that may determine vulvar recurrence, and other clinical determinants besides inadequate excision margins have been suggested, although it is unclear which combination of factors is most significant.[43,75]

Two types of local recurrences, those at the same site as the original (primary) tumor and those at a different vulvar site, were described by Rouzier et al.[76] An analysis of vulvar cancer patients from the Royal Hospital for Women in Sydney showed that primary site recurrences occurred with a median disease-free interval of 21 months, and were associated with a histological margin of 8 mm or less, as reported in several other papers.[40,43,77] "Recurrences" at remote vulvar sites occurred later, with a median disease-free interval of 69 months, and were more commonly associated with lichen sclerosus.[78,79]

As most vulvar squamous carcinomas arise in a background of atypical skin such as HSIL, lichen sclerosus, and dVIN, and as they characteristically recur locally but often at sites remote from the original tumor, it is suggested that many "recurrences" may actually be second primary tumors, which arise in a "field of cancerization"—an area of genetically-altered preneoplastic epithelium that has the predisposition to undergo malignant transformation.[43]

Patients with close (less than 5 mm) surgical margins benefit from postoperative radiotherapy, if it is not possible to re-excise the margins.[80] A study of 205 women with vulvar cancer from Boston reported that margins of 5 mm or less posed the highest risk of vulvar recurrence, and that patients who received a dose of more than or equal to 56 Gy had a lower risk of relapse than those who received less than or equal to 50.4 Gy.[81]

Occasionally, the positive margins may be boosted with brachytherapy, although care must be taken to avoid the risk of necrosis. An alternative is to treat the operative bed with an appositional electron field or conformal external beam irradiation.[27,61]

## 7 | RARE VULVAR MALIGNANCIES

### 7.1 | Vulvar melanoma

Vulvar melanoma is the second most common vulvar malignancy. Any pigmented vulvar lesion should be biopsied or excised for diagnosis, unless it has been present and unchanged for some time.[24] The majority of vulvar melanomas involve the clitoris or labia minora.[27] The Clark or Breslow modifications of the staging system—as included in the American Joint Committee on Cancer (AJCC) system and based on depth of invasion—should be used for the staging of these lesions rather than the FIGO staging system since it is the only system prospectively proven to be correlated with recurrence and survival.[82–84]

Surgery is the treatment of choice for vulvar melanomas. Lesions should be treated by radical wide local excision, with margins around the lesion of at least 1 cm.[27] The current trend leans toward more conservative resection of vulvar melanomas because no survival difference has been found in patients undergoing local excision versus those with radical vulvectomy.[85]

The role of lymph node dissection is also controversial and, to date, no survival advantage has been shown for inguinal lymphadenectomy,[84] although the Intergroup Surgical Melanoma Program's prospective, multi-institutional randomized trial of elective node dissection versus observation for intermediate thickness cutaneous melanomas (1–4 mm) revealed that elective node dissection resulted in a significantly better survival for patients aged 60 years or younger, patients with tumors 1–2 mm thick, and patients with no tumor ulceration.[86]

Sentinel lymph node evaluation has also been explored for vulvar melanoma, and although it is feasible, a false-negative rate of 15% has been reported[87]; it has been suggested that the procedure may increase the risk of locoregional recurrences,[88] and therefore it is not current standard practice.

### 7.2 | Bartholin gland cancer

Bartholin gland carcinomas are rare forms of vulvar malignancy and it is unclear what proportion is associated with high-risk HPV infection. Cancers of the Bartholin glands may be either transitional cell or SCC that arise from the duct, or adenocarcinomas arising from the glands themselves. There are also adenoid cystic and adenosquamous variants. All SCCs showed diffuse and intense p16 expression consistent with the presence of HPV.[89] The diagnosis is often made after resection of a persistent or recurrent Bartholin cyst.[27]

Bartholin gland carcinomas are effectively treated with a radical hemivulvectomy and bilateral groin dissection; however, due to the location of these tumors, deep in the ischiorectal fossa, adequate surgical margins are difficult to achieve and postoperative radiation may decrease the likelihood of local recurrence.[90]

Radical wide local excision alone is adequate treatment for adenoid cystic lesions, and adjuvant radiation is recommended for positive margins or perineural invasion.[91]

### 7.3 | Paget disease of the vulva

Extramammary Paget disease is rare, and can affect the apocrine glands of the vulva. There are two types: the primary form begins as an intraepithelial lesion, but the secondary form is due to invasion from an underlying adenocarcinoma, which may be anorectal, urothelial, or genital tract carcinoma (e.g. endocervical or endometrial).[92]

Vulvar Paget disease occurs predominantly in postmenopausal women who present with vulvar pruritus and pain and, on examination, an eczematoid weeping lesion is often seen.[24] Diagnosis is usually confirmed by biopsy, which will also help to differentiate between an intraepithelial and an invasive lesion.[24]

The treatment of choice for intraepithelial Paget disease is wide local excision. It is challenging to achieve clear margins as histological changes often extend far beyond what is visible macroscopically; even with adequate margins, recurrence rates are high. Due to the high recurrence rate and surgical morbidity, there is a current move to perform less radical resection for intraepithelial lesions, with re-excision at a later date should lesions recur.[93] Lesions involving the urethra or anus also present a management challenge, and may require laser therapy.[6] Another conservative treatment option is local imiquimod.[93] A Cochrane meta-analysis that investigated treatment options concluded that there was no "best" intervention for vulvar Paget disease.[94]

If an underlying adenocarcinoma is present, treatment should be radical wide local excision with margins of at least 1 cm. Inguinofemoral lymphadenectomy should be performed, with adjuvant radiation for the same indications as for squamous carcinomas.[95]

## 8 | PATHOLOGY CONSIDERATIONS

In relation to specimen analyses, the following should be noted:

1. Orientation: correct orientation of the surgical specimen is important.
2. Photographs: these should be taken of the whole specimen, as well as the origin of each tissue block.
3. Measurements: size of the specimen, dimensions of any visible tumor, macroscopic tumor-free margins, and tumor depth (sections taken through the tumor). Sections should also be taken from urethral, anal, and vaginal resection margins.[27]
4. Lymph nodes: these should be dissected out, the site from which they are removed recorded, and a full cross-section of each lymph node should be embedded.[27]

The following histological points should be noted:

1. Tumor type.
2. Depth of invasion: measured from the epithelial–stromal junction of the adjacent dermal papilla to the deepest point of invasion by the tumor.
3. Tumor grade.
4. Histological measurement of tumor-free margins and statement as to whether the tumor is completely excised.
5. Presence or absence of perineural or vascular space invasion.
6. Nature of the adjacent squamous epithelium, e.g. dVIN, lichen sclerosus, and HPV-associated changes.
7. Sites and number of nodes examined, number of positive nodes, and presence or absence of extracapsular extension.[27]

### AUTHOR CONTRIBUTIONS

LR and MC contributed equally in designing, planning, reviewing literature, manuscript writing, and updating references.

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## CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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