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Cancer of the vulva: 2021 update

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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 4% of gynecological 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, and prevalence of HIV).[3-6]

Kang et al.[2] in an epidemiologic study that included 13 high-income countries noted a significant 14% overall increase in incidence of vulvar cancer. This increase was not evenly distributed across age groups; in women younger than 60 years, the overall incidence increased by 38%, whereas there was no significant increase in women older than 60 years of age.

2 | ANATOMY

The external genitalia comprise the vulva and the mons pubis or pubic area. The vulva is in the anterior triangle of the perineum. The elements that make up the vulva include the labia majora and minora, 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.

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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 vagina 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. In addition, 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] who were not initially infected with high-risk HPV types or types included in the vaccines, with vaccine efficacies of more than 90%.[13] 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.[14]

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.[15] In addition, there should be early evaluation of any patient with symptoms (e.g. chronic vulvar pruritus) or signs (e.g. pigmented lesions, irregular ulcers), who may be a candidate for skin biopsy.[16]

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.[17]

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[18]:

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.[6,19] 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.[1,3,9,20]

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 few 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.[21-23]

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. Surgical treatment was previously restricted to excision of scars in women where scarring had led to functional impairment.[24] In a recent review, Eshtiaghi et al.[25] indicated the potential benefit of mesenchymal stem cells including adipose-derived stem cells and autologous platelet-rich plasma in the treatment of lichen sclerosus. Highlighted in the review were several published observational studies including case reports, case series, and cohort studies all showing favorable outcomes regarding symptomatology control in women with lichen sclerosus treated with mesenchymal stem cells injection.[26-32]

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

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: (a) VIN, warty type (b) VIN, basaloid type (c) VIN, mixed	HSIL
Differentiated VIN	VIN, differentiated type	Differentiated VIN (dVIN)

[a]Source: Hoang et al.,[21] Bornstein et al.,[22] Sideri et al..[23]

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.[33,34]

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 ablation e.g. with 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 multifocal 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.[35] There is very little evidence of the effectiveness of topical treatment for HSIL among immunocompromised women.[35] Independent of chosen treatment and margin status, there is risk of recurrence (up to 30%–40%). Therefore, close follow-up is recommended for at least 2–3 years.[33]

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.[36]

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 location (closer to the midline 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.[20,36,37] The FIGO staging of vulvar carcinoma was revisited and changed in 2009 by the FIGO Committee for Gynecologic Oncology.[17,38] However, although nicely done, the 2009 staging was not easy for care providers to use especially for patients with Stage III disease. The substaging was rather nebulous. Furthermore, the FIGO Committee for Gynecologic Oncology now has access to the prospectively collected US National Cancer Database (NCDB) via collaboration with the American Joint Committee on Cancer (AJCC) and the American College of Surgeons. As a result, the Committee decided to update the staging for vulvar cancer.[39] NCDB vulvar cancer data collected over 7 years (2010–2017) was utilized in defining the new FIGO vulvar cancer staging (Table 2). This new staging is applicable to most malignancies arising from the vulva, except melanoma.

4.3 | Histopathological types

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

- Basal cell carcinoma
- Verrucous carcinoma
- Adenocarcinoma related to extra-mammary Paget's disease

TABLE 2 New (2021) FIGO staging for carcinoma of the vulva

Stage	Description	
I	**Tumor confined to the vulva**	
	IA	Tumor size ≤2 cm and stromal invasion ≤1 mm[a]
	IB	Tumor size >2 cm or stromal invasion >1 mm[a]
II	**Tumor 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	**Tumor of any size with extension to upper part of adjacent perineal structures, or with any number of nonfixed, nonulcerated lymph node**	
	IIIA	Tumor 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[b] lymph node metastases >5 mm
	IIIC	Regional[b] lymph node metastases with extracapsular spread
IV	**Tumor 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[b] lymph node metastases
	IVB	Distant metastases

[a]Depth of invasion is measured from the basement membrane of the deepest, adjacent, dysplastic, tumor-free rete ridge (or nearest dysplastic rete peg) to the deepest point of invasion.[51,52]

[b]Regional refers to inguinal and femoral lymph nodes.

- Bartholin gland carcinoma (squamous, adenocarcinoma, or transitional cell carcinoma)
- Sarcoma

4.4 | Histological grades

- GX: Grade cannot be assessed
- G1: Well differentiated
- G2: Moderately differentiated
- G3: Poorly or undifferentiated

4.5 | Treatment

The treatment of vulvar cancer depends primarily on histology and staging. Other variables influencing management are age, existence 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.[40] Management should be individualized, and carried out by a multidisciplinary team in a cancer center experienced in the treatment of these tumors.[36,37,41] 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.[37,41-45] Psychosexual counselling services should be available to all women with preinvasive and invasive vulvar disease from diagnosis, throughout their treatment, and thereafter.

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 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.[17]

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.[17]

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.[46,47]

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.[48] 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.[48-50] Additionally, PET-CT might be used with larger tumors when metastatic disease is suspected or in the recurrence scenario, particularly when exenteration is contemplated.[37]

6 | SURGICAL MANAGEMENT OF VULVAR SQUAMOUS CELL CARCINOMA

Surgical management of vulvar cancer should be individualized, and the most conservative operation that will result in cure of the disease should be performed.[46,47]

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.[36,37,41,43,46,47]

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. Depth of invasion is measured from the basement membrane of the deepest, adjacent, dysplastic, tumor-free rete ridge (or nearest dysplastic rete peg) to the deepest point of invasion.[51,52] These lesions should be managed with radical wide local excision, and groin node dissection is not necessary.[46]

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, ultrasound, or cross-sectional radiological assessment.[20,36]

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.[53-55] 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.[56] 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.[36,46] With most tumors, primary closure is possible, but consideration should be given to reconstructive surgery for closure of large defects, and for maintenance of vaginal function. When reconstruction is necessary, three of the most commonly utilized flaps include the V–Y flap, rhomboid flap, and gluteus maximus myocutaneous flap.[57]

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.[58] The current standard involves resection of the primary tumor and lymph nodes through separate incisions.[37] This approach allows better healing compared with en bloc resection of the vulva and groins.[59] Both inguinal and femoral nodes should be removed, as inguinal node dissection alone is associated with a higher incidence of groin recurrence.[60] While some reviews have suggested that radiation alone can control microscopic groin disease,[61,62] a small randomized trial suggested that groin dissection, with postoperative irradiation for patients with positive nodes, is superior to groin irradiation.[63]

All women who have Stage IB or resectable 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.[37,46]

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.[64]

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.[8,65]

Indications for a sentinel node procedure, as per the GROINSS-V study,[65] 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 and radiologically negative groin nodes

Sentinel lymph nodes are identified using both radio-labelled technetium and blue dye.[65,66] Recently, indocyanine green dye used with near infrared florescent technology has become an option for sentinel node detection.[67]

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.[65]

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.[37,68]

A particular scenario in early disease is in the management of patients with positive groin nodes. The Gynecologic Oncology Group protocol 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.[69,70] 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.[71]

Several studies have demonstrated the prognostic importance of the number and size of groin node metastases, as well as the presence of extracapsular spread.[72-74] 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.[73-75] 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.[36]

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] Data from GROINSS-V II were presented at the European Society for Medical Oncology (ESMO) annual meeting in 2019. Interim analysis showed an increase in groin lymph node recurrence in cases with sentinel lymph node metastasis >2 mm or extranodal extension. After the protocol was amended, adjuvant radiotherapy was given to patients with sentinel lymph node metastasis ≤2 mm whereas inguinofemoral lymphadenectomy was done in cases with sentinel metastasis >2 mm or extranodal extension. The authors concluded that groin radiotherapy is a safe alternative to inguinofemoral lymphadenectomy in cases of vulvar cancer ≤4 cm with sentinel lymph node metastasis ≤2 mm.[76]

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.[77] Sometimes, brachytherapy can be added as a boost to anatomically amenable primary tumors.

There are several 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.[37,77]

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. Underdosage 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.[36]

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 underdosage of the target is substantial, these techniques are best utilized by clinicians who have the necessary expertise.[36,37]

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.[36,37,77]

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.[78]

6.3 | Advanced vulvar cancer

Advanced vulvar cancer includes tumors that extend beyond the vulva, and/or where there are bulky positive groin nodes.[36] 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.[36,37,41,43] 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.[79]

If there are no suspicious nodes either clinically or on imaging, bilateral inguinofemoral lymphadenectomy may be performed; if the nodes are negative, radiotherapy to the groins and pelvic nodes will not be necessary. However, if histology reveals positive nodes, then adjuvant radiotherapy or chemoradiotherapy to the groin and pelvis should be offered as for early-stage disease.[77]

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.[37,61,62,77]

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.[80] 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 radiotherapy, with or without chemosensitization. If there is an incomplete response to radiation, the nodes may then be resected if appropriate.[81] An alternative strategy is the use of neoadjuvant chemotherapy with cisplatin or carboplatin and paclitaxel, to shrink the nodes prior to radiotherapy.[82]

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.[46]

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.[83,84]

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.[85-89] 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.[36,37,77]

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.[90,91] 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.[36,77]

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.[36,77]

6.3.1 | Targeted therapies

There are a host of possible targets for molecular therapies in vulvar squamous carcinoma. Some studies are focusing on aberrant cell cycle activity, while others are looking at extracellular regulators of cellular activity, such as epidermal growth factor receptor (EGFR) and inhibitors of angiogenesis. Possible targets in HPV-associated cancers may be the E6 and E7 HPV oncogenes, as with the therapeutic vaccines, as well as immune-based therapies, while mutations in non-HPV-associated cancers, such as PI3K, CDKN2A, and PTEN, may be effective targets for treatment.[92] Inhibition of EGFR has been successfully utilized and published for vulvar cancer.[93,94] In a phase 2 study, erlotinib, an EGFR inhibitor, showed a clinical benefit rate of 67% in women with metastatic vulvar cancer.[94]

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.[56,95]

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.[96] 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.[53,56,97] "Recurrences" at remote vulvar sites occurred later, with a median disease-free interval of 69 months, and were more commonly associated with lichen sclerosus.[98,99]

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.[56]

Patients with close (less than 5 mm) surgical margins may benefit from postoperative radiotherapy, if it is not possible to re-excise the margins.[100] A study from Boston of 205 women with vulvar cancer 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.[101]

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.[36,77]

6.5 | Recurrent disease

The management of recurrent disease is often difficult, and treatment options depend on the site(s) of the recurrence, the performance status of the patient, and what previous treatment has been given, as well as the findings of re-staging investigations. Options for treatment include surgery, (chemo)radiation, neoadjuvant or palliative chemotherapy, a targeted agent (if available), or best supportive care.

6.6 | Follow-up

Local recurrences most often occur in the first 2 years after treatment, and most women with gynecological malignancies are seen every 3–6 months for the first 2 years, and then every 6–12 months until they are 5 years post treatment. The surveillance visit should include a review of symptoms relevant to recurrence or adverse effects of treatment, and thorough clinical examination.[102]

Elevated pretreatment serum concentrations of squamous cell carcinoma antigen (SCC-Ag) may be an independent prognostic factor for disease-free and overall survival in vulvar cancer patients.[103] For a select group of vulvar cancer patients, SCC-Ag may be used as a serum tumor marker for surveillance.

7 | RARE VULVAR MALIGNANCIES

7.1 | Vulvar melanoma

Vulvar melanoma is the second most common vulvar malignancy, although it is a very rare tumor with an incidence of 0.1 in 100 000. Mucosal melanomas, found on the vulva and in the vagina, have a poor prognosis with a 15% 5-year survival; their cause and genetics differ from cutaneous melanomas.[104] Any pigmented vulvar lesion

should be biopsied or excised for diagnosis, unless it has been present and unchanged for some time.[33] The majority of vulvar melanomas involve the clitoris or labia minora.[36]

There is a lack of consensus on the staging of mucosal melanomas, although most prefer to use the American Joint Committee on Cancer (AJCC) system, which includes the Clark level, Breslow thickness, ulceration, and spread. The Clark or Breslow modifications of the staging system—as included in the AJCC system and based on depth of invasion—should be used for the staging of these lesions rather than the FIGO staging system since the former is the only system prospectively proven to be correlated with recurrence and survival.[105-107]

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.[36] 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.[108]

The role of lymph node dissection is also controversial and, to date, no survival advantage has been shown for inguinal lymphadenectomy,[107] 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.[109] It is important, however, to remove any lymph nodes which clinically or on imaging are involved with tumor.[104]

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[110]; it has been suggested that the procedure may increase the risk of locoregional recurrences,[111] and therefore it is not currently the standard of care. The Melanoma Focus Guideline does not recommend the use of the sentinel node procedure outside of a clinical trial.[112]

Vulvar melanomas should be tested for c-kit and BRAF mutations, as there may be a role for immunotherapies such as nivolumab.[113]

7.2 | Bartholin gland cancer

Bartholin gland carcinomas are rare forms of vulvar malignancy accounting for about 5% of vulvar cancers, 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 gland itself. There are also adenoid cystic and adenosquamous variants. All SCCs showed diffuse and intense p16 expression consistent with the presence of HPV.[114] The diagnosis is often made after resection of a persistent or recurrent Bartholin cyst.[36]

Bartholin gland carcinomas are effectively treated with a radical hemivulvectomy and bilateral groin dissection; however, they are more likely to have metastatic disease at presentation. Due to their location deep in the ischiorectal fossa, adequate surgical margins may be difficult to achieve and postoperative radiation may decrease the likelihood of local recurrence.[115]

Radical wide local excision alone is adequate treatment for adenoid cystic lesions, and adjuvant radiation is recommended for positive margins or perineural invasion.[116]

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).[117]

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.[33] Diagnosis is usually confirmed by biopsy, which will also help to differentiate between an intraepithelial and an invasive lesion.[33]

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.[118] Lesions involving the urethra or anus also present a management challenge, and may require laser therapy.[6] Another conservative treatment option is local imiquimod.[118] A Cochrane meta-analysis that investigated treatment options concluded that there was no “best” intervention for vulvar Paget disease.[119]

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.[120] Women with Paget's disease of the vulva should have long-term follow-up in a specialist vulvar clinic.

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.[36]

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.[36]

The following histological points should be noted:

1. Tumor type.
2. Depth of invasion: measured from the basement membrane of the deepest, adjacent, dysplastic, tumor-free rete ridge (or nearest dysplastic rete peg) to the deepest point of invasion.
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.[36]

AUTHOR CONTRIBUTIONS

AO and LR updated the previous review written by LR and MC. All authors contributed to the development of the current review and approved the final version.

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This chapter reworks and updates the information published in the FIGO Cancer Report 2015 by Hacker et al.[36]

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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