Vulvar cancer: epidemiology, clinical presentation, and management options

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Epidemiology: Vulvar cancer can be classified into two groups according to predisposing factors: the first type correlates with a HPV infection and occurs mostly in younger patients. The second group is not HPV associated and occurs often in elderly women without neoplastic epithelial disorders.

Histology: Squamous cell carcinoma (SCC) is the most common malignant tumor of the vulva (95%).

Clinical features: Pruritus is the most common and long-lasting reported symptom of vulvar cancer, followed by vulvar bleeding, discharge, dysuria, and pain.

Therapy: The gold standard for even a small invasive carcinoma of the vulva was historically radical vulvectomy with removal of the tumor with a wide margin followed by an en bloc resection of the inguinal and often the pelvic lymph nodes. Currently, a more individualized and less radical treatment is suggested: a radical wide local excision is possible in the case of localized lesions (T1). A sentinel lymph node (SLN) biopsy may be performed to reduce wound complications and lymphedema.

Prognosis: The survival of patients with vulvar cancer is good when convenient therapy is arranged quickly after initial diagnosis. Inguinal and/or femoral node involvement is the most significant prognostic factor for survival.

Keywords: vulvar cancer, HPV infection, radical vulvectomy, groin dissection, sentinel lymph node biopsy, overall survival

Introduction

Vulvar cancer is the fourth most common gynecologic cancer and contains 5% of all malignancies of the female genital tract (after cancer of the uterine corpus, ovary, and cervix).¹⁲ There are several histological types, whereas squamous cell carcinoma of the vulva is the most common category (95%), followed by melanoma, sarcoma, and basalioma.³ The survival rate and the relapse-free time correlate with specific histologic growth patterns, as explained below. The prognosis is good if vulvar cancer is diagnosed at an early stage. The correct treatment option for vulvar cancer is important because of its strong influence on sexuality. In recent years, a lot of changes have been made concerning the treatment of vulvar cancer: more conservative, less radical, and more individualized surgery followed by enhanced psychosexual outcomes. Regular prevention followed by early detection and histological examination of any suspicious vulvar lesions help to detect vulvar cancer in the early stages and reduce consecutively morbidity and mortality.

Vulvar anatomy

The vulva is comprised of the female external genitalia, which include the labia majora and minora, clitoris, vestibule, vaginal introitus, and urethral meatus. The vulva serves...
to direct urine flow, prevent foreign bodies from entering the urogenital tract, as well as being a sensory organ for sexual arousal. The internal pudendal artery and, to a lesser extent, the external pudendal artery are responsible for the blood supply. The ilioinguinal and genitofemoral nerve innervates the anterior part of the vulva, whereas the posterior part is innervated by the perineal branch of the posterior cutaneous nerve. The majority of the vulva is drained by lymphatics that pass laterally to the superficial inguinal lymph nodes. The clitoris and anterior labia minora may also drain directly to the deep inguinal or internal iliac lymph nodes (Figure 1).

Epidemiology
Vulvar cancer can be distinguished into two separate diseases: the first type involves a human papillomavirus (HPV) infection that causes vulvar intraepithelial neoplasia (VIN), a predisposing factor for vulvar cancer. Early studies analyzed tissue samples from 48 patients with vulvar cancer. HPV DNA was identified by polymerase chain reaction (PCR) in 48% of explored cases, of which 96% were from subtypes 16 and 18. An estimated 80% of untreated women suffering from VIN III develop invasive vulvar cancer. This kind of vulvar cancer mentioned above often occurs in younger patients (35–65 years of age), and a recent review pointed out that approximately 15% of all vulvar cancers develop in women under age 40. Other predisposing factors, eg, condylomata or sexually transmitted diseases (STD) in the past, low economic status, or nicotine abuse, have also been found.

The second type of vulvar cancer includes vulvar non-neoplastic epithelial disorders (VNED) and advanced age that lead to cellular atypia and eventually to cancer. Elderly patients (55–85 years), in particular, show a low rate of HPV infections and consequently seldom any association with cervical neoplasia. Diabetes mellitus, hypertension, and obesity seem to correlate with the incidence of vulvar cancer, but do not appear to be responsible. Lichen sclerosus, a subgroup of VNED, is mooted as a predisposing risk factor in the development of HPV-negative vulvar cancer. Because of a severe pruritus caused by the lichen, the “itch–scratch cycle” leads to a squamous cell hyperplasia and over time a progression to atypia, followed by VIN and eventual invasive cancer.

Clinical features
The most commonly described symptom of vulvar cancer is a long history of pruritus. Less frequently reported symptoms include vulvar bleeding, dysuria, discharge, and pain.
The most obvious manifestation of vulvar cancer is a vulvar lump or mass, which may present ulcerated, leukoplakic, fleshy, or warty. 

**Histology**

Squamous cell carcinoma (SCC) accounts for approximately 95% of malignant tumors of the vulva and can be grouped into three main histological subtypes of vulvar SCC: warty, basaloid, and keratinizing. The predominant type, keratinizing, accounts for 65%–80% of vulvar SCCs; the basaloid and warty types of SCC account for the remaining 20%–35%. The keratinizing type usually occurs in postmenopausal women; the warty/basaloid types tend to occur more often in premenopausal or perimenopausal women. The keratinizing type is usually formed by well or moderately differentiated cells with an absence of koilocytosis. Figures 2–4 show the histology of a keratinizing SCC and the transition to normal vulvar epithelia. Even with immunohistological staining, the secure differentiation between tumors already invading the stroma for more than 1.0 mm and those invading less than 1.0 mm is not possible.

The warty or basaloid types of SCC are often associated with a VIN. The basaloid type typically grows in bands, sheets, or nests within a desmoplastic stroma, and focal cytoplasmic maturation and keratinization may be observed. The warty type exhibits invasion as bulbous or irregular jagged nests, often with prominent keratinization.

Vulvar melanoma is the second most common neoplasm of the vulva. The majority of lesions involve the clitoris or labia minora. Any pigmented lesion on the vulva should be excised for diagnosis unless it has been known and unchanged for many years. Other histological subtypes include verrucous carcinoma, basal cell carcinoma, giant cell carcinoma, acantholytic SCC, Bartholin’s gland cancer, and Paget’s disease.

**Staging**

Vulvar cancer is staged using the American Joint Committee on Cancer TNM staging system and the International Federation of Gynecology and Obstetrics (FIGO) staging systems (Table 1). These two systems are very similar; both classify vulvar cancer on the basis of three factors: the size of the tumor (T), whether the cancer has spread to lymph nodes (N), and whether it has spread to distant sites (M). The staging system for vulvar cancer is built on surgical data since 1988. The final diagnosis is dependent upon thorough histopathologic evaluation of the operative specimen (vulva and lymph nodes). Various modifications have been made over the years, with a subdivision of stage I added in 1994. The FIGO staging was last reviewed in 2009 by the FIGO Committee on Gynecologic Oncology, to give better prognostic distinction between the particular stages and to guide the clinical treatment more exactly.

Staging reflects the characteristics of vulvar cancer growth that develops in the following way: first, by direct
expansion into the contiguous organs (the vagina, urethra, and anus), followed by lymphatic metastasis to regional lymph nodes (from the inguinal to the femoral to the pelvic lymph nodes), and finally by hematogenous spread to distant sites (liver, lungs, and bones). The risk of nodal metastasis increases with the stage of disease, the size of lesion, and the depth of invasion, and these are the most important prognostic factors for vulvar cancer.24,25

There is no role for diagnostic imaging in the primary detection and characterization of vulvar cancer. However, imaging (MR) may play a role in evaluation of the local extent of disease in advanced cases, especially if urethral invasion is suspected, as well as in the evaluation of lymphadenopathy (US, CT, MRI) and distant metastatic disease (CT and PET CT).27 Using the ultrasound, vulvar cancer appears as a soft tissue mass with internal vascularity. On CT, vulvar cancer appears as a nonspecific soft tissue mass, and on MRI, the tumor shows intermediate signal intensity on T1W and high signal intensity on T2W sequences.

### Table 1 Staging vulvar cancer (TNM and International Federation of Gynecology and Obstetrics, FIGO)

<table>
<thead>
<tr>
<th>TNM categories</th>
<th>FIGO stages</th>
<th>Definition</th>
<th>Surgery</th>
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<tbody>
<tr>
<td>TX</td>
<td></td>
<td>Primary tumor cannot be assessed</td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>IA</td>
<td>No evidence of primary tumor</td>
<td></td>
</tr>
<tr>
<td>Tis</td>
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<tr>
<td>T1a</td>
<td>IA</td>
<td>Lesions 2 cm or less in size, confined to the vulva or perineum and with stromal invasion 1.0 mm or less</td>
<td>WLE, no LNE</td>
</tr>
<tr>
<td>T1b</td>
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<td>Lesions more than 2 cm size or any size with stromal invasion more than 1.0 mm, confined to the vulva or perineum</td>
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<td>T2</td>
<td>II</td>
<td>Tumor of any size with extension to adjacent perineal structures (lower/distal 1/3 urethra, lower/distal 1/3 vagina, anal involvement)</td>
<td>Modified radical vulvectomy (hemivulvectomy, anterior or posterior vulvectomy), LNE bilateral</td>
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<tr>
<td>T3</td>
<td>IVA</td>
<td>Tumor of any size with extension to any of the following: upper/proximal 2/3 urethra, upper/proximal 2/3 vagina, bladder mucosa, rectal mucosa or fixed to pelvic bone</td>
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<td>N1</td>
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<td>M1</td>
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Abbreviations: WLE, wide local excision; LNE, lymphonodectomy; FIGO, International Federation of Gynecology and Obstetrics.

### Treatment

#### Surgical therapy

Historically, the gold standard for even a small invasive carcinoma of the vulva was radical vulvectomy with removal of the primary tumor with a wide margin followed by an en bloc resection of the inguinal and, frequently, the pelvic lymph nodes. This operation showed a high morbidity rate with approximately 50% of wound infections and postoperative complications. The extensive nature of the operation and the inevitable distortion of the appearance of the perineal area can lead to major problems for the patient concerning relationship, sexual function, and, consequently, body image and self-assurance. Accordingly, in most large centers, the traditional en bloc resection has been replaced by the so-called triple incision. Besides the vulvectomy dissection-shape incision, two separate incisions in the groin area are made for inguinal LNE. This procedure shows a markedly lower rate of wound-healing disorders.28

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Management of the primary lesion

In order to avoid psychosexual morbidity, a radical wide local excision is possible in the case of localized lesions. T1 lesions with no extension to adjacent perineal structures (ie, urethra, vagina, and/or anus) might be treated by wide local excision. This operation is as effective as radical vulvectomy in preventing local recurrence.\textsuperscript{10–12} Table 1 shows the tumor size and the recommended operative procedure.

Radical vulvectomy implies removal of the entire vulva down to the level of the deep fascia of the thigh, the periosteum of the pubis, and the inferior fascia of the urogenital diaphragm. A tumor-free margin $\geq 1$ cm is required since a smaller margin is associated with an increased local recurrence risk. This was shown in a retrospective series of 135 patients that found a lower rate of local recurrence in cases with a normal tissue margin of $\geq 1$ cm compared with $<$8 mm (0% versus 50%).\textsuperscript{31} Radical vulvectomy is often performed in connection with either a unilateral or a bilateral groin node dissection. In some cases, a modified radical vulvectomy (including hemivulvectomy) can be performed, which means that only the anterior, posterior, left, or right part of the vulva is removed. T2 lesions with extension to adjacent perineal structures should be treated by radical vulvectomy or hemivulvectomy, as mentioned above. The important oncologic principle remains the same: adequate excision margins to all sides and deep to the tumor.

If the tumor involves the urethra, the distal 1 cm can be excised without affecting continence. Otherwise, if more than the distal 1 cm of the urethra must be excised, the patient will require an additional procedure to prevent urinary incontinence. In some cases, this might be an anterior exenteration with formation of a neobladder.

For patients with a tumor at or close to the surgical margins (\(\leq 8\) mm), a re-excision is suggested, or at least an adjuvant radiation therapy for those who do not want to undergo another surgical procedure.\textsuperscript{31,34}

In some cases of extensive vulvar cancer, plastic surgery is recommended for covering the defect. The multidisciplinary team working with plastic surgery colleagues enhances the spectrum of available operative therapy using local fasciocutaneous skin-flaps (eg, medial-thigh flap, pudendal-thigh flap, or inferior-gluteal flap) for minor cosmetic defects. In cases of more severe wounds extending over larger areas of the vulva and its surrounding regions, regional myocutaneous skin-flaps (eg, rectus abdominis myocutaneous [RAM] flap, gracilis myocutaneous [GMC] flap, or tensor fascia lata [TFL] flap) lead to good results.\textsuperscript{35} Patients receiving a reconstruction after radical vulvectomy show a lower rate of wound dehisences, vaginal intromital stenosis, sexual dysfunction, and urinary problems, compared with those having radical vulvectomy without reconstruction.\textsuperscript{36}

Management of lymph nodes

Inguinofemoral lymphadenectomy is the standard approach for evaluation of the lymph nodes in women with vulvar cancer. An inguinal node dissection alone is associated with a higher incidence of groin recurrence.\textsuperscript{37} Historically, pelvis lymph nodes were also removed, but with an incidence of 2%, pelvic lymph node metastases are quite rare in the early stages of vulvar cancer (T1/T2).\textsuperscript{38} Consequently, pelvic lymphadenectomy is recommended only in the following cases: 3 or more positive unilateral groin lymph nodes, capsule rupture, or macrometastasis $>10$ mm. Groin node dissection is performed to assess nodes for evidence of metastasis, which may indicate the need for further therapy and to help reduce the chance of recurrence of further metastasis. The groin nodes are the most important prognostic indicator in SCC of the vulva.\textsuperscript{26,39}

The indication for lymphadenectomy depends on the stromal invasion. Infiltration of $<1$ mm is not associated with inguinal node metastases, whereas a tumor thickness $>1$ mm should be treated using at least an ipsilateral inguinofemoral lymphadenectomy or a sentinel lymph node biopsy in the case of inconspicuous groins.\textsuperscript{30} Bilateral groin node dissection should be performed for midline tumors and for those involving the anterior labia minora.\textsuperscript{40,41} Large lateral tumors should probably also have bilateral dissection, and definitely if the ipsilateral nodes are positive.\textsuperscript{41} Figure 5 shows the treatment of groin nodes.

Sentinel lymph node (SLN) biopsy is still a new, not yet standardly used treatment, investigating the first potentially metastasized lymph node. SLN biopsy is recommended in those patients who have early stages of vulvar cancer to avoid the operative morbidity that is caused by inguinofemoral lymphadenectomy, such as wound complications or lymphedema.\textsuperscript{42} SLN biopsy may be used in early tumor stage (I or II) and if there are suspicious inguinal–femoral lymph nodes clinically and sonographically.\textsuperscript{43} SLN mapping was originally used to identify regional lymph node metastases in breast cancer and cutaneous melanoma and has now been established in patients with early stage vulvar cancer.\textsuperscript{44,45} The SLN can be detected using injected radio colloid 99mTc (technetium) and isosulfan or methylene blue, which are inserted around the lesion before operation.\textsuperscript{46} A handheld
gamma detection device is used to identify the sentinel lymph node(s). It is estimated that only 25%–30% of patients with early stage vulvar cancer have lymph node metastases. If the sentinel node is positive, a full inguinal lymphadenectomy followed by postoperative radiation therapy is recommended. If the sentinel lymph nodes identified by mapping are histologically negative, no further treatment is indicated. Even though sentinel lymphadenectomy seems to be attractive also for vulvar cancer on account of the highly relevant postoperative morbidity of a systematic inguinofemoral lymphadenectomy. Unfortunately, however, groin recurrences after sentinel lymphadenectomy alone have been reported in various publications. Even though the sentinel procedure is performed only in the early tumor stage, morbidity with a 2.3% rate of groin recurrence has been shown by van der Zee et al. Since in the meantime prospective data on this topic have become available, sentinel lymphadenectomy can be considered an alternative to systematic bilateral inguinofemoral lymphadenectomy in cases of vulvar cancer when the patients are informed adequately. Treatment approach Depending on the results of surgical staging, women are categorized as having early or advanced stage disease: 1) Early stage disease is defined as stage I or II. These patients should undergo a surgical excision including adjuvant treatment based on the findings at the time of surgery. 2) Locally advanced stage disease is defined as stage III or IVA. Operative treatment is preferred whenever feasible. Patients who are not surgical candidates should receive primary chemoradiation. 3) Stage IVB disease includes women with distant metastases – a primary chemotherapy is recommended, provided patients are candidates for systemic treatment. If not, palliative care is appropriate. Radiation Primary radiochemotherapy For patients who are candidates for chemotherapy, chemoradiation might be preferred, according to the data for cervical cancer. In cases of anorectal, urethral, or bladder involvement, tumor that is fixed to the bone or gross lymph node involvement, chemoradiation is recommended. Cisplatin mono, 5-FU, or also mitomycin C in combination with radiation therapy should be performed. In some cases, surgery is possible after chemotherapy and radiation because of reduced tumor mass.
Chemotherapy and new biological agents

Except for the neoadjuvant setting, chemotherapy for vulvar carcinoma is palliative and often ineffective; however, the most frequently used chemotherapy regimens are platinum-based, meaning they consist of cisplatin, given alone or in combination with another agent, such as 5-Flouracil, paclitaxel, vinorelbine, or mitomycin C.88,89 Because of the small number of cases becoming necessary for a chemotherapy, there is no standard treatment yet. The actual response rate to these chemotherapies is low. Therefore, it is important to focus on new biological agents, such as gefitinib and erlotinib, which seem to have good results: gefitinib (Iressa) and erlotinib (Tarceva) are oral, reversible tyrosine kinase inhibitors. These enzymes are associated with the human Epidermal Growth Factor Receptor (EGFR).89 By inhibiting the tyrosine kinase, gefitinib and erlotinib prevent EGFRs from stimulating the uncontrolled growth of cells that contributes to tumor growth. Gefitinib combined with trastuzumab has been investigated in a human vulvar carcinoma cell line (A431) and seems to increase radiosensitivity.61

Neoadjuvant radiation

Even though fewer data are available, patients who are unable to undergo an operative treatment should receive primary radiation therapy (RT). The total dose of radiation should be between 60 Gy and 70 Gy, and both the inguinal and the pelvic regions bilaterally should be treated if there is positive nodal involvement.62 In addition, RT can be used in the preoperative setting for women who present with advanced vulvar cancer. High rates of tumor shrinkage and complete responses at the time of surgery have been reported.

Adjuvant radiation

Radiotherapy of the inguinal and pelvic lymph drainage pathways or a pelvic lymphadenectomy in combination with an inguinal radiotherapy are recommended in cases with 3 or more afflicted lymph nodes together with macrometastases >10 mm and a capsule rupture – this proceeding was the gold standard for a long time.63 Since the ASCO 2012, the indication for adjuvant radiation of the lymph drainage pathways has been enlarged: radiotherapy is already being discussed for patients with just one afflicted inguinal lymph node, as well as for R1 resection or marginal R0 resection without further surgical options.64

A variety of radiation techniques can be selected depending on the patient’s conformation and scope of disease. Treatments should always be based on three-dimensional planning using high-quality CT or MRI images. Combined photon and electron techniques are often used to treat the regional nodes. In recent years, some clinicians have begun to use intensity-modulated radiation therapy (IMRT) or other inverse-planned, computer-controlled delivery techniques, which use computer-generated 3-D images to show the size and shape of the tumor and reduce radiation effects in collateral skin and soft tissue in the same way.

Prognosis

The prognosis of patients with vulvar cancer is quite good when convenient treatment is provided in a timely manner. Inguinal and/or femoral node involvement is the most significant prognostic factor for survival in patients with vulvar cancer.32,35 Extracapsular growth of lymph node metastases, two or more affected lymph nodes, and more than 50% replacement of lymph nodes by tumor are predictors of poor survival. The overall 5-year survival rate ranges from 70% to 93% for patients with negative nodes and from 25% to 41% for those with positive nodes.65 Other prognostic factors include stage, capillary lymphatic space invasion, and older age.32,66 Table 2 shows the survival rates depending on the FIGO stage. Recurrent lesions in the lymph nodes, as well as in distant sites, are not amenable to surgery or radiotherapy. They are difficult to treat, and the 5-year survival rate is generally less than 5%.67

Disclosure

The authors report no conflicts of interest in this work.

References


