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Chapter 15

Cancer of the Vulva — A Review

Fernando Anschau and Manoel Afonso Guimarães Gonçalves

Additional information is available at the end of the chapter

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Abstract

Cancer of the Vulva: a review In reporting on cancer of the vulva, we should keep in mind some important aspects of its epidemiology and its early detection. Most of the papers on the subject refer to vulvar cancer as a rare disease, accounting for 4 to 5% of all malignant neoplasms of the female genital tract and less than 1% of women's cancers. The incidence varies from 1 to 3.6 cases per 100,000 women, with peak incidence at ages 70-79 years. Even though the incidence increases with age, the proportion of young patients with vulvar cancer has greatly increased due to its association with infection with human papillomavirus (HPV). The risk of developing cancer of the vulva is related to behavioral, reproductive, hormonal and genetic aspects. Factors that increase risk include other genital cancers, chronic inflammatory diseases of the vulva, smoking, history of genital warts and vulvar intraepithelial neoplasia (VIN). We can consider that, given the epidemiological evidence, there are two etiologic pathways for vulvar cancer: one related to older patients, in the seventh or eighth decades of life, associated with mutations in TP53 and non-neoplastic epithelial disorders such as chronic inflammation or vulvar lichen, shows precursor lesions of differentiated VIN; the other is more common in young patients, accounts for approximately 43-60% of squamous carcinoma of the vulva, is associated with HPV infection, and is a common precursor lesion of VIN. Eighty-five to ninety percent of vulvar cancers are squamous in origin (squamous cell carcinoma); however, when considering the embryological origin of the vulva - the three germ layers - different histologic types can compose neoplasms affecting the region.

Keywords: Vulvar cancer, clinical presentation, staging, treatment, prognostic factor, review, signs and symptoms, therapy, innovations

1. Introduction

In reporting on cancer of the vulva, we should keep in mind some important aspects of its epidemiology and its early detection. Most of the papers on the subject refer to vulvar cancer as a rare disease, accounting for 4–5% of all malignant neoplasms of the female genital tract

and less than 1% of women's cancers. The incidence varies from 1 to 3.6 cases per 100,000 women, with peak incidence at ages 70–79 years. [1, 2, 3, 4] Even though the incidence increases with age, the proportion of young patients with vulvar cancer has greatly increased due to its association with infection with human papillomavirus (HPV). 5 The risk of developing cancer of the vulva is related to behavioral, reproductive, hormonal, and genetic aspects. Factors that increase risk include other genital cancers, chronic inflammatory diseases of the vulva, smoking, history of genital warts, and vulvar intraepithelial neoplasia (VIN).

We can consider that, given the epidemiological evidence, there are two etiologic pathways for vulvar cancer: one is related to older patients, in the seventh or eighth decades of life, associated with mutations in TP53 and non-neoplastic epithelial disorders such as chronic inflammation or vulvar lichen, and shows precursor lesions of differentiated VIN; the other is more common in young patients, accounts for approximately 43–60% of squamous carcinoma of the vulva, is associated with HPV infection, and is a common precursor lesion of VIN. [6, 7, 8, 9]

Eighty-five to ninety percent of vulvar cancers are squamous in origin (squamous cell carcinoma); however, when considering the embryological origin of the vulva – the three germ layers – different histologic types can compose neoplasms affecting the region. Melanoma is the second most common and should be discussed separately because of its peculiar characteristics.

Prognosis is strongly related to lymph node status and the stage of disease, reaching 90% survival for early stages without lymph node involvement.[1, 10]

Various important advances in the treatment of vulvar cancer were made in recent decades toward more conservative surgery without compromising survival and toward reduction of comorbidities, such as: (1) conservation of the vulva in patients with unifocal tumors, and normal vulva in other aspects; (2) omission of inguinal lymphadenectomy in patients with T1 tumors and stromal invasion <1 mm; (3) elimination of routine pelvic lymphadenectomy; (4) use separate incisions for inguinal dissection; (5) use of preoperative radiotherapy in selected cases; and (6) postoperative radiotherapy to reduce inguinal recurrence in patients with multiple compromised inguinal lymph nodes.

2. Clinical presentation

The diagnosis is often delayed, since vulvar cancer does not show specific signs and symptoms, and older patients do not usually examine their vulva preventively and report their symptoms. Vulvar cancer may be asymptomatic, but the majority of patients present with nodules or vulvar ulcer. Such signs may be accompanied by pain, but it may also be absent. The long-standing pruritus is frequent and may be associated with vulvar dystrophy. Secretions and bleeding are symptoms that are occasionally present, as well as dyspareunia and burning sensation. Putrid odor due to tissue necrosis may also be diagnostic. Enlarged lymph nodes, especially in the inguinal region, denote disease in later stages.[1, 10, 11] A study of delayed diagnosis showed that in 88% of patients, symptoms were already present for about 6 months

and in 28% for more than 5 years. In the same study, emphasis was placed on clinical suspicion in view of symptoms, since 31% of patients had office visits three or more times, but only 25% of cases had undergone biopsy. [12]

As previously mentioned, vulvar melanoma will be addressed separately, but any pigmentation of the vulva deserves attention for diagnosis.

3. Screening

There is no standard procedure for screening for vulvar cancer. However, we must maintain a level of suspicion when seeing patients with signs and symptoms related to the vulvar region and to be attentive to the examination of the female genitalia at check-ups. Patients with history of vaginal and cervical cancer should have the vulva inspected, with or without colposcopy (vulvoscopy), as part of a regular follow-up. Similarly, those with lichen sclerosus or VIN history deserve regular monitoring.

4. Gynecological examination

The vulvar cancer can arise in any region of the vulva, but the most common locations are labia (80%), clitoris (10%), and frenulum region (10%). Most tumors are unilateral, but may present as bilateral or multicentric (Figures 1, 2, and 3). Any malignant neoplastic lesion involving the vagina and the vulva should be classified as vulvar cancer.

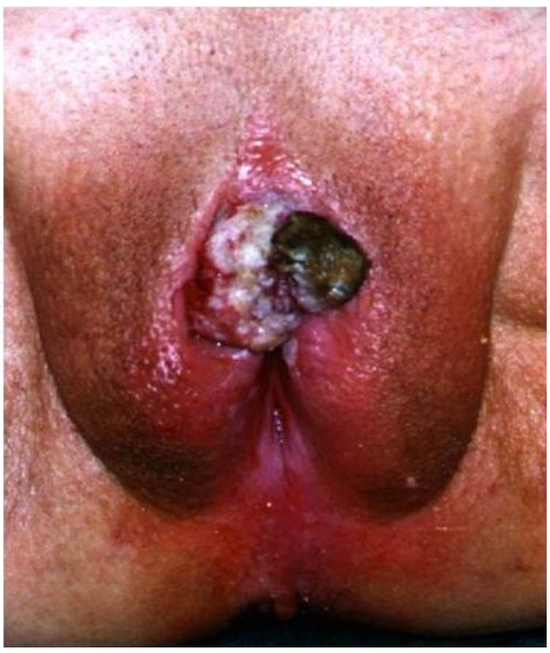


Figure 1. Squamous cell carcinoma of the vulva – clitoral region with involvement of labia minora and majora.

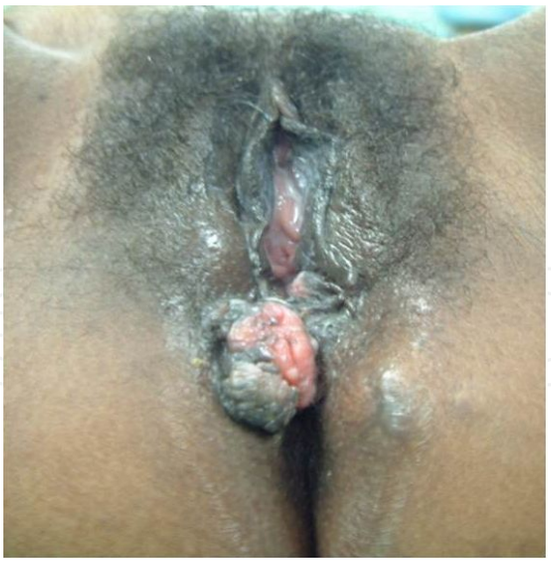
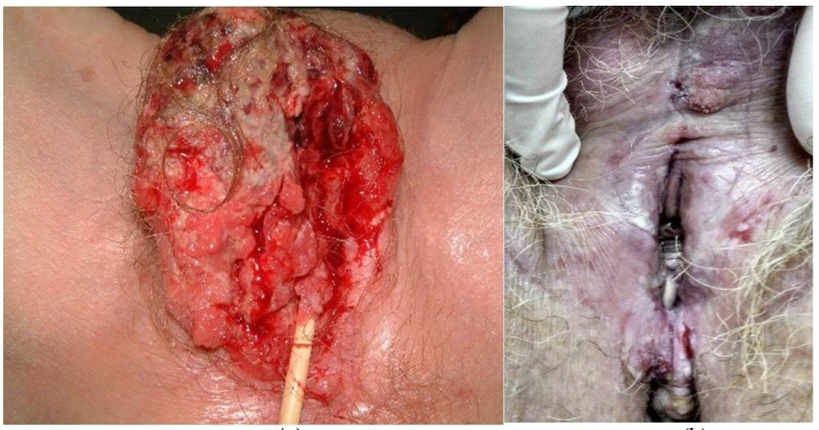


Figure 2. Adenocarcinoma of the vulva – frenulum region extending to the top of the right thigh.



(a) (b)

Figure 3. (a) Squamous cell carcinoma of the vulva with destruction of vulvar anatomy. (b) Carcinoma of the vulva associated with lichen sclerosus Presence of white areas, cracks, macules, plaques, thin and hypochromic skin, and tumor infiltrating next to the clitoris.

On the basis of this knowledge, a careful inspection of the vulva and vagina are important points in the gynecological examination and may include vulvoscopy and colposcopy. Suspicious areas with color changes, redness, ulcers, papules, macules, erosions, thickening of skin, bumps, and cracks must be observed carefully. The lesions may grow and form infiltrating endophytic or exophytic tissue with the formation of visible tumors. When identifying suspicious areas, a histological examination should be performed by biopsy that includes not only the skin but also the subepithelial stroma. Multifocal lesions require multiple biopsies for the investigation of histological changes (Figure 3.1).

Considering that a significant proportion of vulvar cancers are related to HPV infection, especially in younger patients, the vagina (again) and the cervix should be examined. The

cytological examination of the cervix should be carried out according to the current screening parameters. Cytology of the vulva – depending on its collection and proper laboratory analysis – achieves a sensitivity of 95% and specificity of 64% 13; although there is no clear reason to recommend it, it would make the biopsy much more effective. In addition to the inspection, palpation of the genitals, anal/rectal region, pelvic walls, and inguinal regions should be performed. 14 Collins' test (based on toluidine blue staining) was used to demonstrate nuclear changes reacting with toluidine blue; however, the method is non-specific and has not been used in the diagnosis of cancer. The use of acetic acid can highlight lesions and their dimensions, but does not adequately differentiate benign from malignant lesions (Figures 4 and 5).

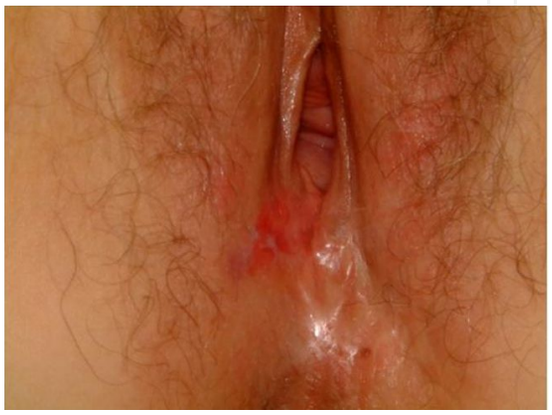


Figure 4. Macula next to right labium majora

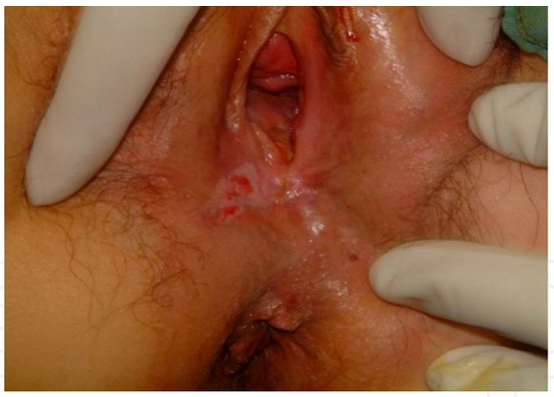


Figure 5. After application of 2% acetic acid – acetowhite lesion with more defined edges (biopsy-confirmed VIN)

5. Staging

The staging system of cancer of the vulva has changed in recent years and since 1988 has become surgical. The final diagnosis and therefore the stage classification depends on the histopathological evaluation of the surgical specimen (vulva and lymph nodes). The classifi-

cation of the International Federation of Gynecology and Obstetrics (FIGO) was last changed in 2009 by the FIGO Committee on Gynecologic Oncology and provides a good discrimination between prognosis and stages (Table 1). [15] The International Union for Cancer Control (UICC) provides a classification for tumor (T), lymph nodes (N), and metastasis (M) (TNM classification), which is shown in the following text compared to the FIGO classification (Table 2). [16]

FIGO Stage		Description
I	Tumor confined to the vulva	
	IA	Lesions ≤2 cm in size, confined the vulva or perineum and with stromal invasion ≤1.0mm[a], no nodal metastasis
	IB	Lesions >2 cm in size or with stromal invasion >1.0mm[a], confined to the vulva or perineum, with negative lymph 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 lymph nodes	
	IIIA	(i) with 1 lymph node metastasis (≥5 mm), or (ii) with 1–2 lymph node metastasis(es) (<5 mm)
	IIIB	(i) with 2 lymph node metastasis (≥5 mm), or (ii) with 3 lymph node metastasis(es) (<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: (i) upper urethral and/or vaginal mucosa, bladder mucosa, rectal mucosa, or fixed to pelvic bone (ii) 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.

Table 1. FIGO classification of cancer of the vulva

TNM	Description
T1	Tumor confined to vulva and/or perineum
T1a	<2 cm with stromal invasion <1.0 mm
T1b	>2 cm with stromal invasion >1.0 mm
T2	Tumor with invasion of the lower part of urethra/vagina/anus
T3	Invasion of the upper part of urethra/vagina, bladder, rectal mucosa, bone, fixation in pelvic bones

TNM	Description
N1a	One or two nodules <5mm
N1b	One nodule >5mm
N2a	Three or more nodules <5mm
N2b	Two or more nodules >5mm
N2c	Extracapsular invasion
N3	Fixed, ulcerated
M0	Absence of distant metastases
M1	Distant metastases
FIGO	**TNM**
FIGO I	T1 N0 M0
FIGO IA	T1a N0 M0
FIGO IB	T1b N0 M0
FIGO II	T2 N0 M0
FIGO IIIA	T1, T2 N1a, N1b M0
FIGO IIIB	T1, T2 N2a, N2b M0
FIGO IIIC	T1, T2 N2c M0
FIGO IVA	T1, T2 N3 M0 T3 any N M0
FIGO IVB	Any T any N M1

Table 2. Staging of cancer of the vulva (FIGO and UICC (TNM))

6. Principles of staging

Cancer of the vulva can spread from the original site by the following: local invasion of adjacent tissues; embolization to regional lymph nodes, usually to the superficial and deep inguinal ones and eventually to the pelvic ones (Figure 6); and via blood, rarely reaching the lungs, liver, and bones. Lymph node involvement is the most important prognostic factor, and lymphatic embolization is the major route of spread.[14] The evaluation of patients with vulvar cancer begins with the physical examination, palpation of inguinal and supraclavicular lymph nodes, vaginal examination, and digital rectal examination. Oncologic cervical cytology, colposcopy of the cervix and vagina (because of the association with squamous intraepithelial lesions), hematological/biochemical tests, and chest X-ray are routine. Cystoscopy and sigmoidoscopy are indicated in suspected cases of bladder or rectal invasion. Pelvic computed tomography

(CT), magnetic resonance imaging (MRI), and intravenous urography can be used to evaluate the possibility of metastatic disease in pelvic lymph nodes or surgical planning.[1, 17]

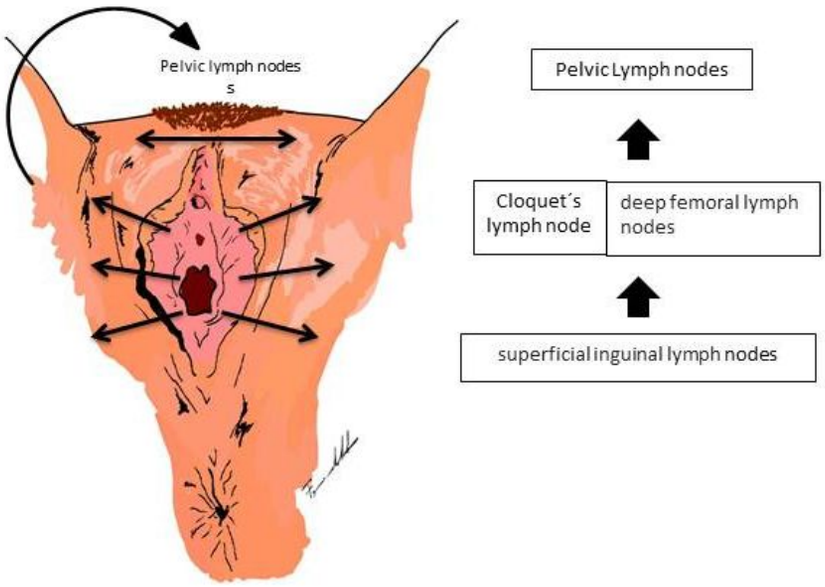


Figure 6. Lymphatic dissemination of vulva

7. Histopathological classification

As mentioned, squamous cell carcinoma is the most common cancer of the vulva, and it is associated with HPV infection especially in younger patients. Melanoma is the second most common vulvar cancer, with approximately 4.8% of these patients; this will be reviewed separately. The other histopathological types of vulvar cancer are verrucous carcinoma, Paget's disease, adenocarcinoma not otherwise specified (NOS), basal cell carcinoma NOS, Bartholin gland carcinoma, and sarcoma.[1]

The three-grade system (G1, well differentiated, G2, moderately differentiated, G3, poorly differentiated or undifferentiated, Gx, grade cannot be accessed) can be used to grade the tumor pathology. In the same aspect, from knowledge of the histopathology, it is important to determine the depth of stromal invasion. 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.[11, 15, 18]

8. Prognostic and recurrence factors

As already discussed, prognosis is strongly related to lymph node status and stage of disease. Positive lymph nodes show a direct correlation with the depth and extent of the invasion. FIGO

staging indicates 5-year survival rates of 90.4% for stage I, 77.1% for stage II, 51.3% for stage III, and 18% for stage IV. Another study of the Gynecologic Oncology Group (GOG) pointed to a 5-year survival rate of 97.9% for tumors with a diameter <2 cm with negative lymph nodes. In this paper, the authors classified patients with vulvar cancer into 4 groups according to histopathological surgical findings (tumor size and extent of lymph node metastases) (Table 3).[19] Other factors with the histological type and the disease-free interval, although they have been considered possible prognostic factors, do not have great clinical relevance. The free surgical margins are the most important predictive factor for local recurrence. Some studies have indicated recurrence rates of 22.5–50% when the disease-free margins are ≤8 mm.[20, 21] In these same studies, the authors demonstrated that in 50% of cases with margins ≤8 mm in histological specimens, margins on macroscopic examination were 1 cm. Thus, a macroscopic tumor-free margin of 1 cm increased to 2 cm for a positive prognosis.[22, 23]

Risk classification	Tumor size/lymph nodes	5-year survival rate (%)
Minimal	Tumor ≤2 cm and negative lymph nodes	97.9
Low	Tumor 2.1–8cm and negative lymph nodes Tumor ≤2 cm and one positive lymph node	87.4
Intermediate	Tumor >8 cm and negative lymph nodes Tumor >2 cm and one positive lymph node Tumor ≤8 cm and two unilateral positive lymph nodes	74.8
High	Tumor >8 cm and two unilateral positive lymph nodes Three or more positive lymph nodes Bilateral positive lymph nodes	29.0

Table 3. Risk groups and survival (GOG)

Women over 50 years of age have a higher risk of vulvar cancer mortality and this risk increases with age. Likewise, a racial disparity in survival has been shown for vulvar cancer, with a poorer prognosis among white patients.

9. Treatment

Surgery is the treatment of choice for patients with vulvar cancer; however, treatment needs to be individualized. Currently, there is no standard surgery, and the emphasis is on finding the most conservative treatment associated with possible cure of the disease. Aimed at decreasing psychosexual morbidity, where possible, a more conservative surgery is sought, such as local excision of the tumor, with tumor-free margin, rather than radical vulvectomy. Surgical removal, to be effective in controlling the disease locally, needs to have lateral margins of at least 1 cm (histologically) and the deep margin should be inferior fascia of the urogenital diaphragm.[1, 24, 25]

With the introduction of radical vulvectomy with en bloc bilateral inguinofemoral lymphadenectomy (butterfly incision), overall survival for vulva cancer went from 20% to 60%, when compared with the simple excision of the tumor. Thus, for a long period, it was the default operation for the treatment of vulvar cancer.[26, 27] Even in the early stages, all patients underwent inguinofemoral lymphadenectomy; although only 20–30% of these showed lymph node metastases. In case of metastasis in inguinofemoral lymph nodes, the best treatment option was pelvic radiotherapy instead of pelvic lymphadenectomy.[28]

En bloc resection (radical vulvectomy with bilateral inguinofemoral lymphadenectomy) is no longer done these days, except in tumors located in the upper regions of the vulva, near the inguinal incisions. This butterfly incision was replaced by triple incision (Figures 7 and 8), which involves the complete excision of the tumor by radical vulvectomy or local excision (with safety margin) and removal of the lymph nodes by two separate inguinal incisions but without the additional skin removal.[1, 23, 25, 29] The triple incision surgery involves less morbidity, with less risk of seroma and lymphedema, as well as lower rate of dehiscence and pain, without increasing the risk of recurrence or mortality compared with en bloc resection.

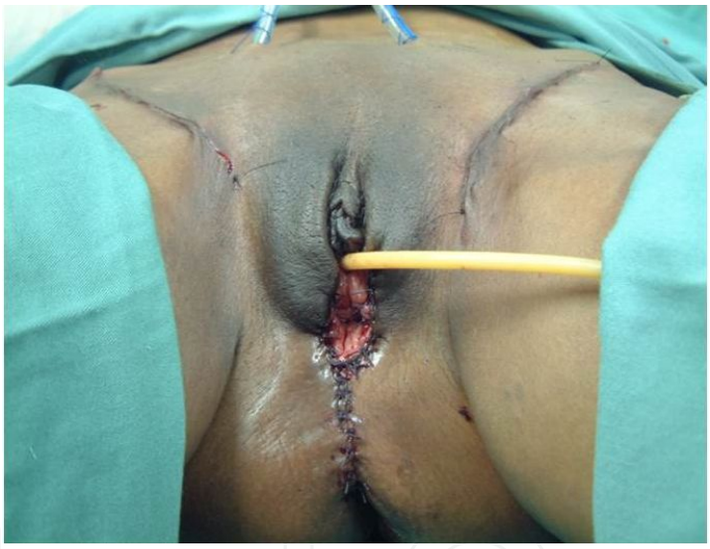


Figure 7. Triple incision (immediate postoperative period) with preservation of the upper part of vulva and clitoris

Patients in stage IA with microinvasive vulvar cancer can be managed with a wide local excision, without the need for inguinal dissection.[30, 31] There is indication of at least ipsilateral inguinal lymphadenectomy in patients with stage IB, II, or any tumor with more than 1 mm stromal invasion.[1] Patients with lateral tumors (in labia majora or minora) without involvement of the midline can be subjected to radical hemivulvectomy, instead of radical vulvectomy, with inguinofemoral lymphadenectomy.

Bilateral inguinal dissection must be performed in patients with tumors in medial regions for those involving the anterior portion of the labia minora and for those with large lateral tumors (>2 cm in diameter, >5 mm of invasion), as well as for patients with positive ipsilateral lymph nodes.[32]

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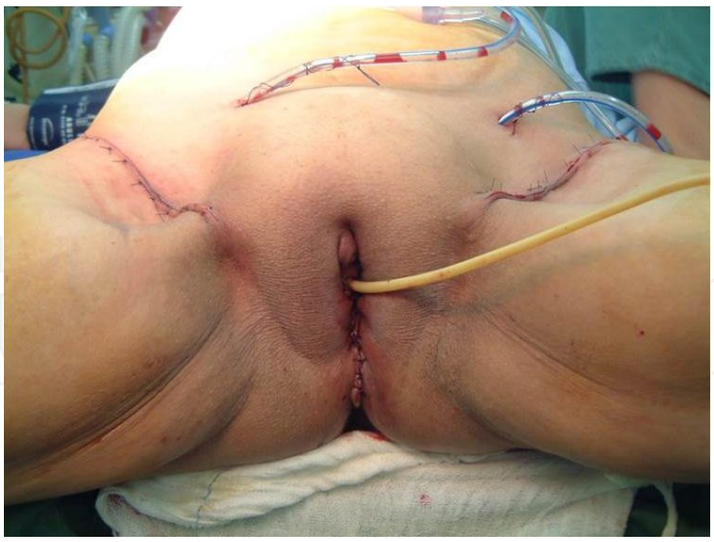

Figure 8. Triple incision (immediate post-operative period) with preservation of clitoris

Patients with FIGO stage III or IV or with extensive involvement of inguinal lymph nodes are considered having advanced disease, for which a multimodal treatment plan should be proposed. Radical vulvectomy combined with partial or total pelvic exenteration is an option for patients with locally advanced disease with clinically resectable lesions.[33, 34]

10. Sentinel lymph nodes

Since only 25–35% of patients with vulvar cancer present with metastasis to lymph nodes, only a small number of patients show a real benefit from inguinofemoral lymphadenectomy. It is therefore evident that alternatives to lymphadenectomy are needed. A sentinel lymph node biopsy has been shown to be a reasonable alternative to complete inguinal and femoral lymphadenectomy in selected patients. In a study of patients with stage I and II with tumor <4 cm, stromal invasion less than 1 mm and clinically negative lymph nodes, sentinel lymph nodes have been shown to have a sensitivity of 94.1% and a negative predictive value of 97.1%. [35] Other studies also demonstrated a sensitivity of 92% and negative predictive value of 97–98%, making sentinel lymph node evaluation an accurate way to stage vulvar cancer.[36, 37] When disease is found in sentinel lymph nodes, or when sentinel lymph node assessment is not possible, bilateral inguinofemoral lymphadenectomy must be performed.

11. Radiotherapy/chemotherapy

Patients undergoing inguinal lymphadenectomy with subsequent identification of a macrometastasis (>5 mm in diameter), extracapsular metastatic spread, or ≥2 micrometastases (<5 mm) should receive bilateral inguinal and pelvic radiotherapy. If the lymph nodes are clinically

positive, one should not proceed with full lymphadenectomy, since the inguinal dissection with postoperative irradiation has the potential to cause severe lymphedema. In these cases, where possible, only the largest lymph nodes should be surgically removed before the patient is subjected to postoperative radiotherapy.[28, 38]

Radiotherapy has also been used preoperatively in patients with advanced disease aimed at providing a more complete surgery. Adjuvant radiotherapy has been added in some studies to decrease local recurrence in patients with positive or slim surgical margins; however, other authors are not of the same opinion.[39, 40]

The use of chemotherapy combined with radiotherapy in the primary treatment of locally advanced carcinoma of the vulva shows better results (regarding clinical response and recurrence) compared to radiotherapy alone. If the primary surgery has the potential to result in an intestinal or urinary tract stoma, it is preferable to employ primary chemoradiotherapy, followed by a more limited resection of the tumor bed, or any residual tumor lesion.[41, 42]

Chemotherapy alone is not a common treatment in primary cancer of the vulva. However, studies have already pointed to the characterization of vulvar cancer as chemosensitive, making chemotherapy a valid alternative for the management of these tumors; but data are still insufficient.[43, 44]

12. Melanoma

Vulvar melanomas occur more frequently in postmenopausal white women. Most patients are asymptomatic except for the pigmented lesion. Most lesions of vulvar melanoma occur on the clitoris or labia minora; it is not unusual for them to extend to the urethra and vagina. FIGO staging for melanoma does not apply, since the lesions are smaller and prognosis is related to the depth of tumor invasion. The system of levels created by Clark or that defined by Breslow may be used to stage melanoma. These systems measure the depth of invasion of the skin. A detailed histological analysis of the surgical specimen is required to carry out these micro-stagings. The staging of melanoma is defined by the system of the American Joint Committee on Cancer (AJCC), which includes other prognostic factors such as primary ulceration of the tumor, number of metastatic lymph nodes, micrometastatic disease based on sentinel lymph node biopsy, sites of distant metastatic disease, and serum levels of lactate dehydrogenase (LDH). Any pigmented vulvar lesions should be biopsied, except when known that there has been no change for several years.[45, 46, 47]

There is a tendency for more conservative treatment of vulvar melanoma. Lesions with less than 1 mm invasion can be simply treated with radical local excision. More invasive lesions require resection of the primary tumor and inguinofemoral lymph nodes. Currently, there is controversy as to the benefit of inguinofemoral lymphadenectomy. [1]

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