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VULVAR CANCER: CLINICAL AND ONCOLOGICAL MANAGEMENT STRATEGIES

CÂNCER DE VULVA: ESTRATÉGIAS DE MANEJO CLÍNICO E ONCOLÓGICO

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ABSTRACT

Vulvar cancer is a gynecological neoplasm with low incidence, yet with significant clinical impact due to its frequently late diagnosis and the morbidity associated with treatment. In recent decades, a shift in its epidemiological profile has been observed, with an increase in cases among younger women, especially related to persistent infection with human papillomavirus (HPV) (OLAWAIYE; CUELLO; ROGERS, 2021; NOGUEIRA-RODRIGUES et al., 2025). Squamous cell carcinoma is the predominant histological subtype and develops through two etiopathogenic pathways: an HPV-dependent pathway, associated with high-grade vulvar intraepithelial neoplasia and a better prognosis, and an HPV-independent pathway, related to lichen sclerosus and differentiated vulvar intraepithelial neoplasia, which is more aggressive (SANCHEZ; RAFFI; KRAUS, 2022). Staging and inguinofemoral lymph node status are key prognostic determinants, reinforcing the importance of early diagnosis (PLANCHAMP et al., 2023). Treatment has evolved toward more conservative and individualized approaches, aiming to reduce morbidity without compromising oncological control (OLAWAIYE; CUELLO; ROGERS, 2021; JHINGRAN, 2022).

Keywords: Vulvar Cancer. Squamous Cell Carcinoma. Human Papillomavirus. Therapeutic Management. Gynecological Neoplasms.

RESUMO

O câncer de vulva é uma neoplasia ginecológica de baixa incidência, porém com impacto clínico relevante devido ao diagnóstico frequentemente tardio e à morbidade associada ao tratamento. Nas últimas décadas, observa-se mudança em seu perfil epidemiológico, com aumento de casos em mulheres mais jovens, especialmente relacionado à infecção

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persistente pelo papilomavírus humano (HPV) (OLAWAIYE; CUELLO; ROGERS, 2021; NOGUEIRA-RODRIGUES et al., 2025). O carcinoma de células escamosas é o subtipo histológico predominante e desenvolve-se por duas vias etiopatogênicas: uma HPV-dependente, associada à neoplasia intraepitelial vulvar de alto grau e melhor prognóstico, e outra HPV-independente, relacionada ao líquen escleroso e à neoplasia intraepitelial vulvar diferenciada, de maior agressividade (SANCHEZ; RAFFI; KRAUS, 2022). O estadiamento e o status linfonodal inguinofemoral são determinantes prognósticos centrais, reforçando a importância do diagnóstico precoce (PLANCHAMP et al., 2023). O tratamento evoluiu para abordagens mais conservadoras e individualizadas, visando reduzir morbidade sem comprometer o controle oncológico (OLAWAIYE; CUELLO; ROGERS, 2021; JHINGRAN, 2022).

Palavras-chave: Câncer de Vulva. Carcinoma de Células Escamosas. Papilomavírus Humano. Manejo Terapêutico. Neoplasias Ginecológicas.

RESUMEN

El cáncer de vulva es una neoplasia ginecológica de baja incidencia, pero con un impacto clínico relevante debido a su diagnóstico frecuentemente tardío y a la morbilidad asociada al tratamiento. En las últimas décadas se ha observado un cambio en su perfil epidemiológico, con un aumento de casos en mujeres más jóvenes, especialmente relacionado con la infección persistente por el virus del papiloma humano (VPH) (OLAWAIYE; CUELLO; ROGERS, 2021; NOGUEIRA-RODRIGUES et al., 2025). El carcinoma de células escamosas es el subtipo histológico predominante y se desarrolla a través de dos vías etiopatogénicas: una dependiente del VPH, asociada a la neoplasia intraepitelial vulvar de alto grado y a un mejor pronóstico, y otra independiente del VPH, relacionada con el liquen escleroso y la neoplasia intraepitelial vulvar diferenciada, de mayor agresividad (SANCHEZ; RAFFI; KRAUS, 2022). El estadio y el estado de los ganglios linfáticos inguinofemorales son determinantes pronósticos centrales, lo que refuerza la importancia del diagnóstico precoz (PLANCHAMP et al., 2023). El tratamiento ha evolucionado hacia enfoques más conservadores e individualizados, con el objetivo de reducir la morbilidad sin comprometer el control oncológico (OLAWAIYE; CUELLO; ROGERS, 2021; JHINGRAN, 2022).

Palabras clave: Cáncer de Vulva. Carcinoma de Células Escamosas. Virus del Papiloma Humano. Manejo Terapéutico. Neoplasias Ginecológicas.

1 INTRODUCTION

Vulvar cancer is a rare gynecological neoplasm, accounting for approximately 4% of malignancies of the female genital tract and with an estimated global incidence of 2.7 per 100,000 women (Olawaiye; Cuello; Rogers, 2021; Nogueira-Rodrigues et al., 2025). Historically considered a disease of postmenopausal women, there is currently an increase in incidence among women under 60 years of age, mainly driven by persistent infection with the human papillomavirus (HPV) (Olawaiye; Cuello; Rogers, 2021).

The etiology of squamous cell carcinoma (SCC), which corresponds to about 90% of cases, follows two distinct pathogenic pathways. The first, associated with high-risk HPV, often occurs in younger women and is linked to usual vulvar intraepithelial neoplasia (uVIN/HSIL). The second route, independent of HPV, affects older women and often develops on chronic dermatoses, such as lichen sclerosus, with differentiated vulvar intraepithelial neoplasia (dVIN) as a precursor and presenting a worse prognosis due to mutations in the TP53 gene (Sanchez; Raffi; Kraus, 2022; Nogueira-Rodrigues et al., 2025).

Early diagnosis is essential, since inguinofemoral lymph node involvement is the most important prognostic factor. However, delay in diagnosis is common, often due to confounding of symptoms with benign inflammatory conditions or lack of adequate physical examination (Planchamp et al., 2023). Therapeutic management has evolved from radical en bloc surgeries, associated with high psychosexual and physical morbidity, to more conservative and individualized approaches, such as radical local excision and sentinel lymph node biopsy (Olawaiye; Cuello; Rogers, 2021).

The present study aims to review the current strategies for the clinical and oncological management of vulvar cancer, discussing everything from staging and initial surgical approach to innovations in adjuvant and systemic treatment.

2 METHODOLOGY

This article was structured as a narrative literature review, with the purpose of compiling and critically analyzing contemporary scientific evidence on the management of vulvar cancer. The literature search was conducted in the PubMed database, using the descriptors "Vulvar Neoplasms" and "Treatment", connected by the Boolean operators AND and OR, following the terminology of Medical Subject Headings (MeSH). Articles published mostly in the last five years, available in full and written in English or

Portuguese, that dealt directly with the therapeutic and diagnostic strategies of vulvar neoplasia, were selected. Exclusion criteria were applied to rule out studies outside the thematic scope, duplicates, and publications with insufficient methodological rigor. The screening of the studies involved the reading of titles and abstracts, followed by an in-depth analysis of the full texts to ensure their relevance, and the data were summarized in a descriptive way.

3 RESULTS

3.1 DIAGNOSIS AND STAGING

The initial evaluation of suspicious vulvar lesions requires biopsy for histological confirmation, with SCC being the predominant subtype. The International Federation of Gynecology and Obstetrics (FIGO) staging system was revised in 2021 to better reflect prognosis, based on tumor size, depth of invasion, and lymph node status (Olawaiye; Cuello; Rogers, 2021). Although FIGO staging is essentially clinical, imaging methods play a fundamental role in the evaluation of tumor extension and therapeutic planning, especially in the analysis of the depth of invasion and the involvement of adjacent structures. (Jhingran, 2022) Preoperative evaluation of inguinofemoral lymph nodes is mandatory for tumors larger than T1a (stromal invasion $\le$ 1 mm), and specialized ultrasonography or magnetic resonance imaging (MRI) is recommended for surgical planning (Planchamp et al., 2023). Magnetic resonance imaging stands out for being superior in the use of contrast agents in the evaluation of soft tissues, allowing a better delimitation of the primary tumor, identification of paravaginal invasion, and differentiation between confined disease and extension to adjacent tissues, and is also useful in the evaluation of recurrence. In addition, positron emission tomography combined with computed tomography (PET/CT) can be used to detect lymph node involvement and distant metastasis, presenting greater sensitivity when compared with computed tomography (CT) alone. (Jhingran, 2022) In addition, Planchmp et al. emphasize that, although there is no recommendation for systematic preoperative lymph node biopsy, the integration between detailed clinical examination and specialized imaging is essential to avoid understaging, especially in tumors larger than 4 cm or with clinical signs suggestive of occult lymphatic dissemination, reinforcing the role of multidisciplinary evaluation in the initial staging.

3.2 Vulvar Cancer Classification Form.

The current classification of vulvar cancer, accepted by the ISSVD (International Society for the Study of Vulvovaginal Disease), recognizes the terms low-grade squamous intraepithelial lesion of the vulva (vulvar LSIL), high-grade squamous intraepithelial lesion of the vulva (vulvar HSIL), and differentiated type vulvar intraepithelial neoplasia. In vulvar intraepithelial lesions, correct terminology and classification is extremely important, as it affects the diagnosis, treatment, and research of cases, impacting the survival of patients (FERNANDES & SÁ, 2019) of the inguinal ligament, known as Cloquet. Most of the vulva drains initially into your superficial sentinel lymph node. Regarding the risk of metastases to the inguinal lymph nodes, it is higher in cases of poorly differentiated neoplasms, with a diameter greater than 2 cm, which have invaded deep into the stroma or lymphovascular space (FERNANDES & SÁ, 2019). It is also noteworthy that the correct distinction between vulvar HSIL and differentiated vulvar intraepithelial neoplasia has a direct impact on the risk of progression to invasive carcinoma, the latter being associated with a faster evolution and a higher risk of local recurrence. (Planchamp et al., 2023)

4 STAGING OF VULVAR CANCER

The staging of malignant neoplasm of the vulva is clinical, radiological, and surgical. (9) Depth of invasion is currently defined as the measurement of the tumor from the basement membrane of the deepest dysplastic/noninvasive epidermal crest, to the deepest point of invasion. (Valença JE, São Paulo; 2016).

Stage I

A tumor confined to the vulva and/or perineum, with negative lymph nodes.

• AI: tumor ≤ 2 cm AND stromal invasion ≤ 1 mm.

• IB: tumor > 2 cm OR stromal invasion greater than 1 mm.

Stage II

Tumor of any size extending to adjacent perineal structures (lower third of urethra, lower third of vagina or anus), with negative lymph nodes.

Stage III

Tumor of any size extending to the upper thirds of perineal structures OR to any number of non-fixed, non-ulcerated regional (inguinal and femoral) lymph nodes.

IIIA: tumor extends to the upper two-thirds of the urethra, vagina, bladder and/or rectal mucosa OR regional lymph node metastases ≤ 5 mm

IIIB: regional lymph node metastases > 5 mm.

• IIIC: regional lymph node metastases With extranodal involvement.

Stage IV

Tumor of any size attached to bone.

• IVA: tumor fixed to the bone and/or fixed or ulcerated lymph nodes.

• IVB: any distant metastasis including pelvic lymph nodes. Hematogenous metastases, when they occur, involve the liver, lungs, and bones.

4.1 EARLY SURGICAL MANAGEMENT OF DISEASE

Radical local excision is the standard treatment for the primary tumor, targeting disease-free margins. Although a margin of 8 mm has historically been sought, recent evidence suggests that smaller margins may be acceptable as long as they are tumor-free, especially to preserve critical structures such as the clitoris and urethra (Planchamp et al., 2023; Nogueira-Rodrigues et al., 2025). In general, surgery should be carefully indicated, since the anatomical proximity to structures such as the urethra, bladder, and rectum can limit extensive approaches, reinforcing the need for conservative surgical strategies whenever oncologically safe. (Jhingran, 2022) Planchamp et al. emphasize that the current trend in the surgical management of early disease is to individualize the extent of surgery, prioritizing functional preservation without compromising oncological control, especially in small lateral tumors, in which conservative surgery associated with adequate lymph node assessment has excellent specific survival rates.

The approach to lymph nodes has undergone significant changes. Sentinel lymph node biopsy (SLN) is recommended for unifocal tumors smaller than 4 cm without clinically suspicious lymph nodes. The GROINSS-V II study demonstrated that, in patients with micrometastases in the LNS ($\le$ 2 mm), inguinofemoral radiotherapy is a safe alternative to complete lymphadenectomy, with lower morbidity and isolated inguinal recurrence rates of only 1.6% at 2 years (Oonk et al., 2021). On the other hand, patients with macrometastases (> 2 mm) in the LNS should undergo inguinofemoral lymphadenectomy, as radiotherapy alone in this population has resulted in unacceptable rates of recurrence (22%) (Oonk et al., 2021). Even in scenarios of initial disease treated surgically, a relevant proportion of patients may require adjuvant treatment, especially in

the presence of compromised margins or lymph node involvement, showing that surgery alone is not always sufficient for oncological control. (Jhingran, 2022) It is reinforced that the adoption of sentinel lymph node biopsy should only occur in centers with proven experience, since technical failures in the identification of the sentinel lymph node are associated with an increased risk of inguinal recurrence. (Planchamp et. al, 2023)

In addition, it was found that the improvement of imaging techniques and radiotherapy planning directly influenced surgical selection. As described by Jhingran (2023), the use of intensity-modulating radiotherapy (IMRT) in locally advanced tumors has made the delimitation of inguinal fields more predictable, reducing complications and providing accurate data to decide between SLN and complete lymphadenectomy.

4.2 LOCALLY ADVANCED AND RECURRENT DISEASE

For diseases involving midline structures (anus, urethra) where surgery would result in loss of function or stomas, primary or neoadjuvant chemoradiation is indicated, achieving high pathological complete response rates and allowing for less mutilating surgeries (Planchamp et al., 2023). Concomitant chemotherapy was incorporated into the management of these patients based on extrapolated evidence of locally advanced gynecological tumors, demonstrating improved overall survival when compared to radiotherapy alone, with cisplatin being the most widely used regimen. External radiotherapy associated with brachytherapy was the pillar of definitive treatment, allowing better local control of the disease and anatomical preservation when compared to extensive surgical approaches. (Jhingran, 2022) In the setting of metastatic or recurrent disease not amenable to surgical or radiotherapy rescue, systemic options are limited. Platinum-based therapies remain first-line, but immunotherapy with checkpoint inhibitors (e.g., pembrolizumab) has shown efficacy in specific subgroups, such as PD-L1-positive tumors or tumors with microsatellite instability (Nogueira-Rodrigues et al., 2025). Local recurrence is relatively frequent, especially in the advanced stages, occurring predominantly in the first two years after initial treatment, and is associated with a poor prognosis. In such cases, MRI plays a central role in the follow-up, allowing the differentiation of tumor recurrence from post-treatment fibrotic changes, whereas positron emission tomography can help in the detection of diseases at a distance. (Jhingran, 2022)

In addition, it was found that the in-depth pathological characterization of advanced lesions helps in therapeutic selection. Sanchez, Raffi, and Kraus (2022) highlight that tumors associated with the HPV-independent pathway have more infiltrative patterns and a greater propensity for recurrence, which justifies greater post-treatment surveillance and, in some cases, wider surgical margins or early multimodal strategies. These findings, together with the expansion of the use of immunological biomarkers, expand the range of tools available to define the treatment of patients with advanced and recurrent disease.

5 DISCUSSION

The evolution in the management of vulvar cancer reflects a continuous effort to balance oncological control with quality of life. The shift from en bloc radical vulvectomies to triple-incision approaches, and later to the sentinel lymph node technique, drastically reduced the incidence of complications such as wound dehiscence and lower limb lymphedema (Nogueira-Rodrigues et al., 2025). In this context, modern therapeutic strategies have also emphasized the individualization of treatment, avoiding extensive interventions when oncologically unnecessary and incorporating less mutilating modalities with comparable results of local control. (Jhingran, 2022)

Thus, it is important to mention that the routine adoption of the sentinel lymph node procedure changed perioperative decision-making and reduced mobity without apparent impairment of regional control in selected populations; therefore, current clinical practice emphasizes the stratification of lymph node treatment based on the size of the metastasis and the preoperative image, favoring radiotherapy in micrometastases and lymphadenectomy in macrometastases, as evidenced by the GROINSS-V II study and reviews of contemporary surgical management (Oonk et al., 2021; Olawaiye; Cuello; Rogers, 2021).

The GROINSS-V II study was a milestone in establishing radiotherapy as a safe treatment for micrometastases, sparing patients from the morbidity of complete lymphadenectomy (Oonk et al., 2021). However, the management of macrometastases remains challenging, and the ongoing GROINSS-V III study seeks to evaluate whether dose-escalation chemoradiation can replace lymphadenectomy in this higher-risk group (Oonk et al., 2021; Planchamp et al., 2023). Recent advances in radiotherapy techniques, including intensity-modulated radiotherapy and image-guided brachytherapy, have allowed greater dose conformation to tumor volume, reducing exposure to adjacent

tissues and, consequently, acute and late toxicity, without compromising oncological control. (Jhingran, 2022) Planchamp et al. reinforce that the incorporation of modern radiotherapy techniques not only improves local control, but also has a direct impact on long-term quality of life, reducing rates of lymphedema, fibrosis, and urinary and intestinal dysfunctions, aspects that are particularly relevant in a population that is often elderly and has multiple comorbidities.

In addition to these changes, and according to Jhingran (2023), the refinement in the delimitation of target volumes and the use of techniques such as IMRT allowed for the reduction of acute and late toxicities in inguinofemoral and pelvic regions, especially in locally advanced chaos. This advance increases organ preservation and reduces the need for extensive surgeries, contributing to better sexual and urinary function. Thus, the integration of radiotherapy reinforces the importance of multidisciplinary approaches in therapeutic planning.

The distinction between HPV-dependent and HPV-independent etiological pathways is gaining more and more prognostic relevance. HPV-independent tumors, often associated with p53 mutations, tend to be more aggressive and have higher rates of local recurrence, requiring close surveillance and possibly wider surgical margins (Planchamp et al., 2023; Sanchez; Raffi; Kraus, 2022). Similarly, the stage of the disease at the time of diagnosis remains the most relevant single prognostic factor, directly influencing recurrence and survival rates, with a higher risk of local failure in the advanced stages. (Jhingran, 2022)

Finally, systemic treatment for advanced vulvar cancer still lacks specific robust clinical trials, often relying on extrapolations of cervical cancer data. The introduction of molecular tests to identify therapeutic targets and the use of immunotherapy represent the current frontier to improve survival in these cases of poor prognosis (Nogueira-Rodrigues et al., 2025). In this scenario, local recurrence remains a relevant clinical challenge, occurring more frequently in the first years after initial treatment and being associated with a poor prognosis, which reinforces the importance of structured follow-up strategies and the judicious use of imaging methods to differentiate between tumor recurrence and post-treatment changes. (Jhingran, 2022) Most recurrences occur in the first two to three years after initial treatment, justifying intensive follow-up protocols during this period, especially in patients with high-risk factors, such as positive lymph node

disease, HPV-independent tumors, and borderline surgical margins (Planchamp et al., 2023)

Furthermore, the literature demonstrates that the management of locally advanced tumors should always be individualized. As highlighted by Planchamp et al. (2023), the decision between primary surgery, chemoradiation, or combined approaches should consider the anatomical extent, anticipated functional impact, and patient expectations. In this sense, Jhingran (2023) reinforces that neoadjuvant chemoradiation may allow less extensive resections in cases that otherwise required highly mutilating surgeries. This therapeutic individualization, therefore, constitutes a central pillar of modern care, aligning oncological efficacy and functional preservation. Finally, it is emphasized that, despite significant advances, vulvar cancer remains a rare neoplasm with a scarcity of specific prospective clinical trials, reinforcing the need for collaborative studies that allow refining therapeutic strategies, validating prognostic biomarkers, and expanding access to innovative systemic therapies. (Planchamp et al., 2023)

6 CONCLUSION

The management of vulvar cancer has evolved significantly, abandoning standardized radical surgeries in favor of an individualized approach that balances oncological control with the preservation of quality of life and sexual function. The implementation of the sentinel lymph node technique and the replacement of lymphadenectomy with radiotherapy in cases of micrometastases represent crucial advances in the reduction of complications such as lymphedema. The distinction between HPV-dependent and independent tumors has been consolidated as a determining prognostic factor. It is concluded that the current therapeutic success depends on a multidisciplinary approach, integrating precision surgery, modern radiotherapy and, in advanced or recurrent cases, new systemic therapies based on molecular profiles.

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