

Review

Therapeutic Approaches to Vulvar Cancer: A Review of Literature

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Abstract

Objective: Vulvar cancer is a rare gynecological cancer that mainly affects postmenopausal women. The aim of this review is to analyze the most recent data available in the literature on the clinical and therapeutic approach to vulvar carcinoma. **Mechanism:** Studies available in the literature on the therapeutic management of patients with vulvar carcinoma until November 2022 have been screened. A comprehensive search was performed in the PubMed (MEDLINE), EMBASE, SCOPUS and Web of Science databases. **Findings in Brief:** The approach to vulvar carcinoma has deeply evolved over the years. The management of early-stage vulvar carcinomas is well established and widely shared, while that of advanced and recurrent cancers is a subject of debate. The assessment of the nodal status has changed from the past with the passage from inguinal lymphadenectomy to the removal of only the sentinel node. **Conclusions:** The gold standard for the management of vulvar cancer is surgery, applicable in the first instance in early-stage tumors and after neoadjuvant therapy for larger tumors. Assessment of the nodal state is crucial and the method to be used depends on the degree of suspicious of positive lymph nodes. The prognosis is good if the treatment is applicable as soon as possible.

Keywords: vulvar cancer; vulvectomy; nodal status; vulvar flap; vulvar surgery; vulvar safe margins

1. Introduction

Vulvar cancer (VC) is a rare gynecological cancer. It mainly affects postmenopausal women, although the average age of incidence has decreased in recent years due to the increase in human papilloma virus (HPV) infections worldwide. From 2001 to 2017, the incidence of vulvar tumors associated with HPV increased by 1.2% per year, while decreases were found in warty (2.7%) and microinvasive (5.5%) carcinomas [1]. The most common histological type is squamous cell cancer.

In 2020, World Health Organization (WHO) identified 45,240 new cases worldwide, with prevalence in Northern America and Western Europe. Therefore, it is possible to define two premalignant types of intraepithelial vulvar cancer: vulvar intraepithelial neoplasia (VIN) related to HPV, which is more common in young women, multifocal and multicentric and VIN associated with vulvar dermatosis, such as lichen sclerosus, more common in older woman and usually monofocal [2,3].

In the minority of cases, VC is asymptomatic and for this reason the diagnosis may be delayed. Usually the symptoms are: vulval pain, pruritus, bleeding and sometimes there is a lump or an ulcer. There is no screening for early detection, therefore the most effective strategy to reduce the incidence of vulvar cancer is the treatment of

predisposing lesions. Any suspected vulvar lesions should be biopsied to exclude out invasion [4]. The dermoscopy can also be extremely useful in carrying out a biopsy as it allows for the selection of the point of greatest suspicion within the lesion. A targeted biopsy with histological examination is necessary to make a definitive diagnosis. The size of the biopsy taken should be at least 4 mm and in patients with multiple vulvar lesions, a separate biopsy of all lesions should be performed and the sampling site should be indicated. Vulvar cancer has always been staged by surgery. The International Federation of Gynecology and Obstetrics (FIGO) has introduced the revised 2021 staging for vulvar cancer. Imaging had no role in FIGO 2009 classification. However, the 2021 revision incorporated cross-sectional imaging findings into vulvar cancer staging, and this staging applies to all types of vulvar cancer except vulvar melanoma [5,6].

Today the treatment of cervical cancer is predominantly surgical and radiotherapeutic [7]. The surgical procedure, however, has been modified over the years in favor of a more personalized and conservative approach [8]. The goal is to reduce post-operative complications (infection, tissue necrosis, pain, functional and esthetic distortion, deterioration of sexual life and of psychological health) by ensuring and maintaining oncologic radicality. In the past, the



approach was a radical vulvectomy with en bloc bilateral inguinal-femoral lymphadenectomy. Now, for the early stage, the surgical approach consists in a modified radical vulvectomy, with surgical lymph node assessment [9]. The urethra, clitoris and anal sphincter are spared. Of course, it is important to assess the state of surgical margins because positive margins are correlated with a higher rate of local recurrence [10]. A recent innovation consists in postoperative reconstruction [11,12]. The main pathway of cancer spread is through the lymphatic vessels, so the mapping of sentinel lymph nodes (SLN) is essential [13,14]. The negativity of these lymph nodes is a positive prognostic factor and correlates with a low recurrence rate and with better overall survival. If the SLN is positive, the tumor is classified as stage III, in fact, the presence of lymph node metastases is the most important prognostic factor with overall 5-year survival decreasing from 95% in the absence of inguinal metastases, to 62% in case of inguinal metastases. Radiotherapy is the main adjuvant therapy in advanced stages, supported by platinum-based chemotherapy [15]. Recent advances include new therapeutic modalities such as immunotherapy [16]. The current therapeutic strategies, customized and conservative, have the aim of extending the patient's expectancy of life, reducing post-operative complications and also of positively impacting psychology and consequently the quality of life (QoL), personal and of the couple.

The aim of this review is to analyze the most recent data available in the literature on the clinical and therapeutic approach to vulvar carcinoma.

2. Materials and Methods

Studies available in the literature on the therapeutic management of patients with vulvar carcinoma until November 2022 have been screened. No time limits for research have been selected and all types of articles in the English language have been included. A comprehensive search was performed in the PubMed (MEDLINE), EMBASE, SCOPUS and Web of Science databases by two authors independently (TGD and IF).

The keywords systematically searched were the following: vulvar cancer OR vulvar tumor OR vulvar neoplasm OR vulvar malignancy AND treatment AND approaches AND nodal evaluation AND treatment. Any disagreement between them over particular articles was resolved through discussion with a third (external) collaborator.

3. Results

In the past, the surgical approach to vulvar cancer was particularly aggressive and included the total bilateral vulvar excision and the bilateral removal of the inguinal lymph nodes. Today the surgical approach is more conservative and precise, tailored on patient case by case, providing the

excision of the lesion with minimal margins of healthy tissue and evaluating the first lymph node draining the area affected by the neoplasia (sentinel lymph node). The revolution in this area is especially appreciable for the reconstructive techniques applied after excisional surgery.

3.1 Early Stage

This category includes lesions with a diameter of less than 4 cm and with a depth of <1 mm (FIGO stage I and II < 4 cm). These tumors do not require lymph node evaluation due to the absence of malignancy after nodal excision and are therefore treated with local excision only; tumors <4 cm and with stromal invasion >1 mm, instead, require more extensive surgery and removal of homolateral sentinel node. More extended tumors (diameter >4 cm or multifocal) are treated with modified radical vulvectomy and lymph node excision. This more invasive approach is burdened with a high rate of intra and post-operative complications. In order to minimize these complications, still ensuring oncological radicalism, numerous authors have conducted studies on the safety of disease-free margins. Currently, the established limit for disease-free margins is 8 mm, however, Milliken *et al.* [10] in 2020 showed that closer margins (2–3 mm) are not associated with a statistically significant difference in recurrence rates [8,10,17]. This approach is even more interesting for the treatment of lesions close to the midline because it would allow the preservation of delicate anatomical structures (clitoris, urethra) thus improving patients' quality of life and sexual functions [18].

Unfortunately, there are no randomized controlled trials (RCTs) available that allow, to date, to affirm the safety of this approach. Indeed, if a disease-free margin <3 mm is found, margin enlargement or the use of adjuvant therapy (radiotherapy) is recommended.

3.1.1 Esthetic Reconstruction

Achieving an acceptable aesthetic outcome should be one of the objectives of the gynecologist oncologist surgeon who deals with vulvar cancer with the aim of improving the patient's psychological acceptance and the aesthetic result. Two flap types are feasible intraoperatively, after excisional vulvar surgery: Transpositional Flap and Advancement Flap. The first category includes: Anterolateral Thigh Flap; Lotus Petal Flap; Gluteal Fold Flap and Gluteal Thigh Flap. The second category includes: Medial Thigh Flap V-Y and Gluteal Fold Flap [19]. These methods provide the movement of portions of tissue from a healthy area, called donor, to the area where the removal of the neoplasm took place, called the recipient. By applying these procedures, it is possible to minimize tissue loss in the vulvar area with a significant increase in post-operative complications and aesthetic satisfaction of the patient. Recently, Giannini *et al.* [11] conducted a study on 62 patients with vulvar carcinoma. With the application of the V-Y gluteal fold advancement flap, the authors demonstrated a significant reduction

in intra- and post-operative complications, a lower rate of positive/close margins and a lower need for adjuvant treatments in V-Y flap patients' group.

3.1.2 Lymph Nodes Assessment

The evaluation of the lymph node is a milestone for the correct staging and, consequently, for the treatment of VC, in fact more than 30% of these tumors have hidden nodal involvement [20–26]. Despite this, poor strong evidences are available about the approach to be used. The detection of sentinel lymph node requires the use of a tracer that shows the first lymph node draining the area affected by the lesion; for this purpose, radioactive tracers, methylene blue dye and indocyanine green are currently used, without the prove of a more efficient marker [27–30]. Conventionally, only the tumor's homolateral lymph nodes are studied, but bilateral lymph node evaluation is required for midline lesions [31]. Sentinel lymph node removal is applicable in tumors <4 cm in diameter, while in larger tumors evidence suggests the use of more invasive surgery albeit burdened by higher intra and peri-operative complications [32]. This approach is also indicated in case of macroscopic positivity of the sentinel node, in case of failure to identify the sentinel node or in presence of bulky lymph nodes [33,34]. The opposite is what concerns the treatment of lymph node micrometastases, in fact, as demonstrated in GROINSS-V-II in 2021, radiotherapy is the best treatment applicable for the management of this eventuality [35].

3.2 Advanced Stage

Vulvar tumors at stage FIGO >II are considered non surgically eradicable in first instance and therefore require neoadjuvant therapy including radiotherapy and systemic chemotherapy. Fortunately, after adjuvant therapy almost all vulvar tumors can be surgically removed and an associated vulvar reconstruction can be performed. Reconstruction, in fact, can improve the prognosis of locally advanced cancer by increasing healthy resection margins [36]. This makes it possible to have a higher rate of first surgery in multidisciplinary centers with plastic surgeons.

Additionally, in case of inguino-femoral lymph nodes negativity, vulvar cancers can benefit from local radiotherapy [37,38]. Suspected lymph nodes on the basis of clinical and radiological examinations should be biopsied and, if positive, require systemic adjuvant therapy. Forner *et al.* [39], have recently demonstrated in a meta-analysis that surgery plus chemo/radiotherapy improves 5-year overall survival of patients with advanced cancer compared to exclusive radiotherapy and that there are no differences between the neoadjuvant approach based on chemo and radiation therapy.

3.3 Treatment of Recurrence

Relapse is diagnosed between 12 and 37% of VC patients, most of whom recurs within 2 years of primary treat-

ment [40]. Risk factors that increase recurrence rates include advanced age, large size of the primary tumor, its wide deep-extension, lymph node positivity, presence of lymph-vascular space invasion (LVSI), excision with non-ideal margins, multifocality and persistence of precancerous lesions [41–44]. Localized recurrence is 20–23% and can be treated with surgery and the excision extent depends on tumor's size [23]. A share between 9 and 38% of VCs recurs at lymph node level and the treatment of these lesions includes surgery associated with radiotherapy, although several studies available in the literature highlight the superiority of a combined approach in terms of improvement of overall survival [44,45].

Finally, distant recurrences, although rare, are burdened by poor prognosis and require systemic therapy.

The treatment of relapses is still debated and several approaches have been proposed. Concerning chemotherapy, platinum-based therapies in combination with paclitaxel appear to be the treatment of choice but existing data in the literature are scarce [46–48]. The use of pembrolizumab and targeted therapy, such as bevacizumab, seem promising but the data available are limited [43,47,49–52].

The approach to recurrence must be multidisciplinary and personalized based on the patient's frailty status and on the characteristics of the primary tumor, as well as of recurrence [53,54].

3.4 Non-Surgical Approach

Treatment of vulvar carcinoma does not only include a surgical approach. In fact, although radiotherapy and chemotherapy play a more important role in the adjuvant treatment of this tumor, they represent a valid alternative for the neoadjuvant treatment and they can be used in selected cases. Chemotherapy and radiotherapy alone or combined are effective in vulvar cancer and can be used as an adjuvant, neoadjuvant or as exclusive therapy. Brachytherapy, instead, is not indicated for the treatment of vulvar cancer [47]. The first-choice chemotherapy for the treatment of vulvar cancer is cisplatin but there are some studies on the use of bleomycin, 5-fluorouracil, mitomycin and carboplatin [48]. Furthermore, Cemiplimab has recently been approved as an immunological therapy. Finally, the use of electrochemotherapy is applicable to the treatment of vulvar tumors, however, their use depends on the localization of the lesion and its extent. Indeed, five or six cycles of chemo are used for adjuvant treatment of vulvar cancer. The use of radiotherapy, instead, is generally limited to the adjuvant treatment of malignant vulvar lesions. The total time of administration depends on the number of Grays (Gy) to be administered, usually 4–5 weeks, and the dose used varies according to the characteristics of the patient and of the tumor, but generally the dose used is between 46–54 Gy. Finally, radio-chemotherapy, chemotherapy or radiotherapy could be used even for palliative treatments.

4. Discussion

The approach to vulvar carcinoma has deeply evolved over the years, with the transition from extensive and disfiguring surgery including wide local excision and hemivulvectomy to a more conservative surgery with better aesthetic and functional results for the patient [55]. In fact, since 1979 it was demonstrated in a study on a small cohort of patients that the application of less invasive surgery was associated with a better quality of life, sexual activity and sexual pleasure [56]. Unfortunately, while the management of early-stage vulvar carcinomas is well established and widely shared thanks to the publications of multicentric studies, that of advanced and recurrent cancers is subject of debate [57–59]. Even the assessment of the nodal status has changed from the past with the passage from inguinal lymphadenectomy (IFLND) to the removal of only the sentinel node, with the aim of avoiding or, at least, minimizing the comorbidities associated with inguinal surgery [60]. The SLN biopsy when applicable (early stage unifocal squamous cell cancer of the vulva (<4 cm) and no suspicious and/or enlarged lymph nodes at imaging) is burdened with a statistically significant lower incidence of complications compared to the more extensive technique. The data supporting this claim come mainly from the study by Oonk *et al.* [35] which reported short- and long-term complications of patients treated with SLN and IFLND; data in fact were all in favor of minimally invasive technique given the significance of reducing rates of cellulitis, lymphedema and wound breakdown.

The European and American guidelines agree on the surgical treatment of primary lesion with wider excision based on the maximum diameter of the tumor; on the need for an adequate anatomical reconstruction and also on the approach to be used for lymph node evaluation (mono- or bilateral SLN for patients without evidence of clinical, radiological or histological nodal disease); moreover, also regarding the treatment of local and lymph-nodal relapse the guidelines suggest similar therapeutic iters while it remains uncertain and, therefore research target, the systemic treatment for distant relapses and metastatic disease (external beam radiotherapy (EBRT) or EBRT with or without brachytherapy and/or concurrent chemotherapy, targeted therapies, immunotherapies) [35,61].

It would be interesting to highlight that, in the future, a molecular classification would allow to refine the management of vulvar cancer with the identification of different risk subcategories and could consent to further tailor the treatment and follow up of this gynecologic cancer [62].

5. Conclusions

In conclusion, the gold standard for the management of vulvar cancer is surgery, applicable in the first instance in early-stage tumors and after neoadjuvant therapy for larger tumors. Assessment of the nodal state is crucial and the method to be used depends on the degree of suspicious of

positive lymph nodes. The prognosis is good if the treatment is applicable as soon as possible and practiced in reference centers, where a multidisciplinary team takes care of the patient and adopts a personalized strategy for each patient. The main objective is the patient's health, obtained by balancing the oncological benefits of radical surgery and the patient's quality of life in order to keep her physical and psychological well-being intact.

Author Contributions

TGD, AG and FT designed the research study. IF, OD and GDB performed the research. IC, CT and AT analyzed the data. GB, IP and GP wrote the manuscript and contributed to data acquisition and analysis. LM and VDD supervised and contributed to interpretation of data for the work. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare no conflict of interest. Ludovico Muzii and Andrea Giannini are serving as the Editorial Board members of this journal. Ottavia D'Oria, Violante Di Donato, Ilaria Cuccu and Andrea Giannini are serving as the Guest editors of this journal. We declare that Ottavia D'Oria, Violante Di Donato, Ilaria Cuccu, Ludovico Muzii and Andrea Giannini had not involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Michael H. Dahan.

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