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Invited Review

Locally advanced squamous cell carcinoma of the vulva: A challenging question for gynecologic oncologists

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HIGHLIGHTS

- Advanced vulvar carcinoma is based on the primary tumor (T3-T4), or on the presence of bulky, fixed or ulcerated nodes.
- Preservation of the bowel and/or urinary function without permanent stomas may require multimodality approaches.
- A personalized approach with RT with/without concurrent chemo and/or surgery may be justified to avoid permanent stomas.
- A multidisciplinary approach is warranted for patients with locally advanced vulvar carcinoma.

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ABSTRACT

Squamous cell carcinoma of the vulva is a rare female malignancy, with an incidence increasing with age. Unfortunately, one third of the patients are diagnosed with locally advanced disease, which constitutes a clinical challenge for the clinicians who treat these patients. The main challenges are represented by: 1. The primary site of the disease, which can be proximal to anatomical structures like the anal canal posteriorly, or the urethra and the bladder anteriorly, that in some circumstances cannot be spared without a bowel and/or urinary stoma; 2. The locoregional nodes that can be involved by the tumor, and they can be bulky, fixed or ulcerated; 3. The clinical condition of the patient, who may carry several comorbidities. Treatment modalities include radiation with or without chemotherapy, and surgery. In order to preserve the bowel and the urinary function without a permanent stoma, a personalized management with a multimodality approach is warranted. In this systematic review, we first clarify the different definitions of "locally advanced vulvar carcinoma". Secondly, we evaluated the different treatment modalities described in the literature, and the impact of the different treatment strategies on prognosis and on preservation of bowel/urinary function. Finally, we offer a possible algorithm that may help the clinicians in treating patients with these uncommon and challenging situations with a multidisciplinary approach.

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1. Introduction

1.1. Epidemiology

Squamous cell carcinoma of the vulva is a rare disease of the female genital tract, accounting for approximately 5% of all the gynecologic tumors. The age-specific incidence ranges from 0.4:100,000 in the thirty-years' population, to 20:100,000 in women older than 70 years old [1]. In the United States, approximately 6020 women have been diagnosed with vulvar cancer during 2017, with 1150 deaths from the disease [2].

1.2. Staging

Vulvar cancer spreads through 3 different routes:

1. Direct extension to the adjacent anatomical structures, such as vagina, urethra and anus
2. Lymphatic dissemination, usually to the regional inguino-femoral nodes. This may occur even in the early stage of the disease
3. Hematogenous dissemination to distant sites, such as lungs, liver and bone, is a rare event that may occur late in the course of the disease.

The staging system reflects these different ways of dissemination. Table 1 reports the 2009 FIGO staging classification [3]. In the 2009 FIGO classification, patients with negative nodes are considered to be at low-risk regardless of tumor size. Therefore, the 1988 stage II (>2 cm) and 1988 stage Ib (< 2 cm) were combined together [3]. In the 2009 classification, tumors of any size involving the lower urethra, lower vagina or anus with negative nodes are classified as stage II (1988 stage III) because of their relatively good clinical outcome. Tumors with positive nodes with or without extension to adjacent perineal structures are still classified as stage III. The number and the characteristics of nodal metastases are taken in account to further subdivide stage III in three subgroups with different prognosis.

Table 1
2009 FIGO staging of vulvar carcinoma.

Stage	
Ia	Tumor confined to the vulva or perineum, ≤ 2 cm in size, stromal invasion ≤1mm*, negative nodes
Ib	Tumor confined to the vulva or perineum, >2 cm in size or stromal invasion ≥1mm*, negative nodes
II	Tumor of any size with extension to adjacent perineal structure (lower urethra, lower third of vagina, anus), negative nodes
III	Tumor of any size with or without extension to adjacent perineal structure (lower urethra, lower third of vagina, anus) with positive groin nodes
$IIIa_1$	Node metastasis (≥ 5 mm) or 1–2 node metastasis/es (< 5 mm)
IIIb	>2 node metastases (≥ 5 mm) or > 3 node metastases (< 5 mm)
IIIc	Node metastases with extracapsular spread
IVa	Tumor invades any of the following: upper urethral and/or vaginal mucosa, bladder mucosa, rectal mucosa, or fixed to pelvic bone, or fixed or ulcerated
IVb	groin nodes. Any distant metastasis, including positive pelvic nodes

* 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.

1.3. Treatment

Surgical management is the cornerstone of treatment for most patients with vulvar cancer, and includes radical local excision or tailored radical vulvectomy with bilateral inguinal lymphadenectomy with separate groin incisions [4–7]. Sentinel node procedure is a safe alternative to lymphadenectomy in patients with a tumor size <4 cm, without clinically suspicious groin nodes. Due to the rarity of these tumors and the expertise that is needed for this procedure, patients should be treated by surgeons with skill in both vulvar cancer and sentinel node mapping [8].

Pelvic lymphadenectomy is not part of the surgical staging. The overall rate of positive pelvic nodes is approximately 5%, with a 15–20% rate in patients with positive groin nodes and nearly 0% in those with negative groin nodes [9]. Furthermore, the results of the Gynecologic Oncology Group [GOG] 37 demonstrated the superiority of postoperative pelvic and groin radiotherapy [RT] versus ipsilateral pelvic node dissection in patients with positive groin nodes after radical vulvectomy and bilateral inguinal lymphadenectomy [10]. The survival benefit for RT was even more significant for those patients with clinically suspected or fixed ulcerated groin nodes as well as for those with two or more histologically positive groin nodes.

1.4. Adjuvant treatment

Postoperative adjuvant inguinal and pelvic RT is warranted in patients with more than one intranodal metastasis or with extra-nodal tumor growth after a full inguino-femoral lymphadenectomy. Another indication for postoperative radiation is the presence of positive margins for invasive disease not amenable of re-excision [6,7]. The radiation volume is adapted to the clinical indication and usually includes the lower pelvic nodes and inguinal nodes for those with positive groin nodes at time of surgery. RT dose should be approximately 50 Gy for patients with microscopic metastases and 60 Gy for those with multiple positive nodes or extracapsular spread [7,11]. In a National Cancer Data Base [NCDB] analysis, the adjunction of adjuvant chemotherapy significantly reduced the risk of death in node-positive vulvar carcinoma patients who received adjuvant RT, with a hazard ratio [HR] of 0.62 [12].

1.5. Prognosis

Lymph nodal status is the strongest prognostic factor for squamous cell carcinoma of the vulva. The 5-year overall survival (OS) rates range from 70 to 98% for patients with negative nodes to 12–41% for those with metastatic nodes. Several studies have demonstrated the prognostic relevance of the number and size of groin metastases, as well as of the presence of extracapsular spread [1,13,14]. The AGO-CaRE-1 retrospective study assessed 1047 patients who underwent

surgery and groin resection for vulvar cancer, of which 370 (35.3%) were found to have positive groin nodes [14]. The ratio of number of positive nodes to the number of resected nodes was an independent prognostic variable for both progression-free survival (PFS) and OS.

Tumor stage is another independent prognostic variable [1,15,16]. Podratz et al. [15] retrospectively evaluated the outcome of 224 patients treated from 1955 to 1975 at the Mayo Clinic, reporting a 5- year OS of 90%, 81%, 68% and 20%, for patients with stages I, II, III, and IV, respectively. In the FIGO Annual Report n. 26, the 5-year OS was 78.5% for patients with stage I, 58.8% for stage II, 43.3% for stage III, and 13.0% for stage IV disease [16]. In a Dutch study on 269 patients treated from 1988 to 2009, 113 (42.4%) patients were reclassified in a lower stage of disease according to the 2009 FIGO classification, and no patients were upstaged. The new staging system provided a better reflection of prognosis [17].

The laterality of nodal metastasis is no longer considered a prognostic variable in vulvar cancer. A retrospective assessment of 468 patients treated at two different Institutions (Mayo Clinic of Rochester and Medical University of Gdansk), showed that bilateral nodal disease did not impact cause-specific survival, justifying it being omitted from the 2009 staging system [18].

2. Aim of the study

At presentation, approximately one third of patients with squamous cell carcinoma of the vulva have locally advanced disease. In these circumstances there is little consensus regarding both the definition and the treatment modality [13,19–21]. Current approaches include ultraradical surgery, exclusive radiation treatment, concurrent chemoradiation [CCRT], and a combination of these treatment modalities. Since a recommended treatment strategy is lacking, and the treatment should be often individualized, we aimed to review the current literature in order to offer a possible algorithm that may help the physicians in treating patients with challenging clinical presentations of vulvar cancer. In any case, due to the complexity of the clinical scenario, patients with locally advanced disease should be referred to tertiary centers, and the treatment strategy should be individualized by a multidisciplinary team.

3. Definition

The term “locally advanced vulvar carcinoma” has been referred to different clinical presentations. These definitions include:

- Large primary tumors extending beyond the vulva or presenting with bulky positive groin nodes [13].
- Tumors either close or involving the neighboring organs: vagina, urethra, bladder, anus and/or rectum. These tumors may also be fixed to the pelvic bones [20].
- Tumors which encroach upon or cross the borders with surrounding structures such as the urethra or anus [21].
- Primary or recurring tumors that cannot be locally managed with a radical vulvar resection [19].

Most of these definitions support the concept that the standard surgical approach including radical excision/vulvectomy and bilateral inguinal lymphadenectomy is not feasible mainly for two reasons:

1. The impossibility to remove the primary tumor with adequate surgical margins
2. The presence of groin nodes fixed to the fascia, muscle, or vascular structures [20]

However, the concept of “resectability” may also depend on both the surgeon skills and the philosophy and the risks that are considerable acceptable for each patient. Thus, an adequate and thorough assessment of the primary site and of the nodal involvement, as well as the performance status (PS) of each patient, is crucial in order to better define the best approach in a multidisciplinary setting.

4. Treatment modalities

Treatment modality of locally advanced squamous cell carcinoma of the vulva largely depends on both the size and location of the primary tumor and the locoregional nodes, and the PS and general characteristics of the patient [20].

4.1. Primary surgery

The surgical resection of primary tumor with free surgical margins and without sphincter damage leading to urinary or fecal incontinence should represent the first option of treatment whenever possible [21]. The radical vulvectomy or modified radical vulvectomy usually consists in three separate incisions: one for the primary tumor and two for the groins' dissection. Resections up to 1.5 cm of the distal urethra to obtain negative surgical margins do not seem to affect the vesical continence [22]. When the disease involves the anus, rectum, rectovaginal septum, proximal urethra or bladder, pelvic exenteration with permanent colostomy and/or urinary diversion may be required. This surgical procedure should be taken into consideration only in carefully selected cases.

Pelvic exenteration or abdomino-perineal excision in combination with vulvectomy and bilateral inguinal lymphadenectomy has been assessed in small series, with a great variability in both oncological outcomes and surgical-related morbidity and mortality [19,21,23–29]. The reconstructive portion of the surgical procedure consists in the closure of the genital area and includes different options: a unilateral/bilateral gracilis myocutaneous flap, or a vertical rectus abdominis myocutaneous flap, or an anterolateral thigh flap, or a deep inferior epigastric artery perforator flap. The reported 5- year OS rates range from 20% to 70%. This variability is strictly related to the different nodal and surgical margin status. Postoperative complications range from 52.6% to 100%, and the perioperative mortality rate ranges from 0% to 20%, but in most series, it is <4%. For instance, Hopkins and Morley [26] reported a 5-year OS of 60% among 19 patients who underwent a posterior (n.14), anterior (n.2) or total (n.3) exenteration for advanced or recurrent squamous cell carcinoma of the vulva. Five-year OS ranged from 71.4% for the patients with negative nodes to 0% for those with positive nodes ($p = 0.002$), and from 63.6% for the patients with primary disease to 37.5% for those with recurrent disease ($p = ns$). No perioperative death occurred, but 10 patients (52.6%) reported severe complications, including vesico-vaginal fistula, entero-cutaneous fistula, conduit leak, small bowel occlusion, stomal hernia, deep venous thrombosis, abscess and postoperative stress urinary incontinence.

Remmenga et al. [25] reported of 5 patients with locally advanced vulvar carcinoma involving the perirectal area, who underwent a radical vulvectomy, bilateral inguinal lymphadenectomy, partial rectal resection with protective colostomy as primary treatment. Four patients agreed to a colostomy closure 6 months after primary therapy and resumed their normal bowel function. All patients were disease-free at the time of publication.

O'Donnell et al. [21] reported of 57 patients with primary advanced vulvar cancer and 13 with recurrent disease who underwent radical ano-vulvectomy at a referral center in UK. Forty-one patients (58.6%) experienced one or more complications, mainly represented by wound breakdown or infective complications. One (1.4%) perioperative death occurred due to myocardial infarction. As far as primary advanced disease is concerned, complete primary closure of the wound was achieved in 21 cases (36.8%), whereas the other patients had the wound left partially or completely open to heal by secondary intention. Overall survival significantly correlated with nodal status and tumor

stage. Median OS was 121 months for patients with negative nodes compared with 19 months for those with positive nodes.

Less radical surgical alternatives have been described for patients with locally advanced disease. Specifically, in patients with anterior extension of the disease, a resection of the urethra and bladder neck with closure of the bladder and diversion with a suprapubic catheter can be accomplished. For those patients who remain free of disease at 6 months, this can be converted to a more permanent diversion using the appendix in many cases, leaving the intact bladder as the reservoir with the aim of reducing morbidity.

Resection of fixed, bulky nodes can be taken in consideration in selected cases. The transposition of the sartorius muscle over the uncovered femoral vessels may help in reducing postoperative complications and hernias. A collaboration with a vascular surgeon can be required if the femoral vein and/or artery need to be respected and substituted with a graft. Again, a cutaneous or myocutaneous flap may be necessary to cover the skin surface.

4.2. Preoperative radiotherapy

Boronow et al. [29] introduced a therapeutic alternative to pelvic exenteration for 48 patients with locally advanced vulvo-vaginal carcinomas. They reported the administration of external-beam RT followed by a surgical resection of the primary tumor and of the inguinal bulky nodes. Five-year OS was 75.6% for the 37 primary cases, and 62.6% for the 11 recurrent cases. One patient underwent total exenteration for local failure, one had a posterior exenteration for local failure, one a urinary diversion and one a bowel diversion because of RT induced fistulas. Therefore, only 4 of 48 patients were eventually diverted, in comparison with 48 patients who would have been diverted if primary exenteration had been performed. Hacker et al. [30] reported of 8 patients with locally advanced vulvar carcinoma who were administered preoperative 44 to 54 Gy external-beam RT to the primary tumor, and one patient received additional 24 Gy intracavitary RT. A significant tumor shrinkage occurred in 7 patients (87.5%), allowing a conservative surgery; in 4 of them (50%) a pathological complete response was obtained. Five patients underwent post-operative groin RT. Five of the 8 (62.5%) were alive with no evidence of disease (NED) after an interval time ranging from 15 months to 10 years.

Rotmensch et al. [31] treated 16 stage III-IV vulvar carcinoma patients with preoperative external RT (40 Gy to the vulva and 45 to the groin and pelvic nodes) followed by radical vulvectomy and inguinal lymphadenectomy. Significant tumor shrinkage was observed in 12 cases (75.0%), with 62.5% of the patients having visceral preservation. Four patients (20.0%) had no major response to RT, and finally underwent urinary or fecal diversion. Four and 2 patients had central and distant relapse respectively, and the cumulative 5-year OS was 45%.

4.2.1. Current utilization

RT has evolved from the 3-dimensional conformal RT (3D-CRT) to intensity modulated RT (IMRT), which is currently the most widely used approach to locally advanced vulvar carcinoma [32,33]. Computed tomography (CT) or magnetic resonance imaging (MRI) is employed to properly define the target volume [7,11]. Combined photon and electron techniques are frequently used to adequately treat the inguinal areas [13]. The RT fields should include the pelvis, groin nodes and vulva, up to a total dose of at least 50 Gy [11,13]. Gross disease may be boosted either with appositional fields of electrons selected to provide an adequate dose to the surface and at depth or with conformal external beam RT, and large vulvar tumors probably require 60–70 Gy to achieve a good local control.

External RT may downsize of the tumor in 70–85% of cases, thus reducing the need for exenteration, although a temporary bowel diversion may be required in some circumstances to better tolerate RT and to avoid the clinical sequelae of bowel fistulas that may occur during the radiation treatment [21]. The surgical approach after neoadjuvant radiation can be extremely complex, because of necrotic areas that need to be removed with the tumor. This would allow a better surgical healing. Furthermore, plastic reconstruction is needed to fill areas with "loss of substance". Postsurgical healing may also be impaired by poor blood supply and tumor necrosis consequent to RT. Surgical complications reported include failure to heal, lymphedema, skin desquamation, wound cellulitis, and bowel and bladder fistulas. These are tremendous consequences that may take up to several months to be overcome.

For these reasons, a primary surgical approach can still be considered as a potentially curative approach in selected patients.

4.3. Concurrent chemoradiation

Based on the good results obtained by combined 5-fluorouracil [5-FU], mitomycin-C [MMC] and RT in anal canal carcinoma, many small-size studies assessed the role of CCRT as primary treatment followed by tailored surgery or as definitive therapy for locally advanced squamous cell carcinoma of the vulva [5,34–48] (Table 2).

Acute toxicities, including moist skin desquamation, moderate to severe neutropenia, and diarrhea, have often been reported within 30 days from the end of the RT. For this reason, some treatment protocols have been planned to divide RT in two courses with an interval of 2 weeks. Severe complications, such as bowel perforation, bowel obstruction, hip necrosis and pubic bone necrosis, have been seldom reported, while wound breakdown is a common complication in patients undergoing surgery after CCRT.

4.3.1. Management of the primary tumor

Thomas et al. [34] were the first who described the use of concomitant chemo (5-FU/MMC)-radiation therapy (CCRT) in 9 patients with primary locally advanced disease. This schedule obtained a complete response in 6 patients (66.7%). After a median follow-up of 16 months, 7 patients (77. 8%) were NED after CCRT alone or followed by local excision of residual or recurrent disease.

In a phase II trial of 5-FU/cisplatin[CDDP]-based CCRT in 12 patients with FIGO stages III-IV squamous cell carcinoma of the vulva, a complete and a partial response were reported in 8 (66.7%) and 3 (25.0%) patients, respectively [35]. Ten (83.3%) patients were NED after a median follow-up of 37 months.

The combination of 5-FU, CDDP and RT in 12 patients was reported by Eifel et al. [38]. Four of them (33%) had a pathological complete response, two patients (17%) had a complete clinical response, not followed by surgery; five patients (42%) had a partial response, and 4 of these developed recurrent disease in the irradiated field. The 2-year OS in the entire cohort of patients was 58%.

Lupi et al. [39] reported on the use of CCRT, using 5-FU/ MMC. This approach achieved a clinical response in 22 of 24 primary cases (91.6%) and in 7 of 7 (100%) recurrent cases. The surgical mortality rate was 13.8%, and the overall recurrence rate was 31.8%.

Landoni et al. described the outcome of 58 patients with primary or recurrent disease, treated with CCRT followed by wide local excision and inguinal lymphadenectomy in 42 cases [40]. A complete pathological response was found in 36.4% of patients with primary neoplasia and in 66.7% of those with recurrent tumor. Interestingly the rate of response of the inguinal nodes was reported: a complete pathological response occurred in 48.0% of the 25 patients with a primary diagnosis, and in 20% of the 5 patients with recurrent disease. For the entire group the 2-year OS was 36%.

Leiserowitz et al. [41] analyzed 23 patients treated with 5-FU or 5-FU/CDDP-based CCRT for locally advanced carcinoma of the vulva with clinically uninvolved groin nodes. Fourteen patients (60.9%) had a complete clinical response. With a median follow-up of 42 months, 14 patients (60.9%) were NED. Interestingly, no patient developed lymphedema, arterial insufficiency, neurological sequelae, or hip necrosis.

Table 2
Concurrent chemoradiotherapy in advanced squamous cell carcinoma of the vulva.

Authors [ref.]	Chemotherapy	Total RT dose	Patients	Response
Thomas [34]	5-FU 1000 mg/m^2 /day c.i. for 4 or 5 days ± MMC 6 mg/m^2 day 1	45–51 Gy	9	cCR: 6 (66.7%)
Berek [35]	CDDP 50 mg/m^2/day 1–2 or CDDP 100 mg/m^2 day 1 or 2 + 5-FU 1000 mg/m^2/day c.i. for 4 or 5 days	44–54 Gy	12	cCR: 8 (66.7%)
Scheistroen [36]	BLEO 30 mg day 1, 3, 5 on week 1 and 3	30–45 Gy	20	cCR: 5 (25%)
Koh [37]	5-FU 750–1000 mg/m^2/day For 3–4 days + CDDP 50–100 mg/m^2 d1 or MMC 10 mg/m^2	40–54 Gy	20	cCR: 10 (50%)
Eifel [38]	CDDP 4 mg/m^2/days 1–4 + 5FU 250 mg/m^2/day c.i. days 1–4 over 4 weeks	40–50 Gy	12	cCR: 6 (50.0%) pCR: 4 (33.3%)
Lupi [39]	5-FU 750 mg/m^2/day c.i. days 1–5 + MMC 15 mg/m^2 day 1	54 Gy	24	cCR: 10 (41.7%) pCR: 8 (33.3%)
Landoni [40]	5-FU 750 mg/m^2/day c.i. days 1–5 + MMC 15 mg/m^2 day 1	54 Gy	52	cCR: 14 (26.9%)
Leiserowitz [41]	5-FU 1000 mg/m^2/day c.i. days 1–4 ± CDDP 100 mg/m^2 day 2	36–54 Gy	23	cCR: 14 (60.9%)[a]
Moore [43]	5-FU 1000 mg/m^2/day c.i. days 1–4 + CDDP 50 mg/m^2 day 1	47.6 Gy	71	cCR: 33 (46.5%)
Han [43]	5-FU 1000 mg/m^2/day c.i. days 1–4 + MMC 10 mg/m^2 or CDDP 100 mg/m^2 day 1	40–62 Gy	14	cCR: 10 (71.4%)
Gerszten [44]	5-FU 1000 mg/m^2/day c.i days 1–4 + CDDP 50 mg/m^2 day 1	44.6 Gy	18	cCR: 13 (72.2%)
Montana [45]	5-FU 1000 mg/m^2/day c.i days 1–4 + CDDP 50 mg/m^2 day 1	47.6 Gy	46	Nodes resectable in 37 (80.4%)[b] pCR on nodes: 15/37 (40.5%)
Gaudinieau [46]	Weekly CBDCA AUC2 (n.11) Weekly CBDCA AUC2 + PTX 60 mg/m^2 (n.2) CBDCA AUC5 + 5-FU 1000 mg/m^2/day c.i. days 1–4 (n.2) RT alone (n.7)	50 Gy	22	pCR on vulva 16 (72.7%) pCR on nodes 6 (27.3%)
Moore [47]	Weekly CDDP 40 mg/m^2	57.6 Gy	58	cCR: 37 (63.8%) on vulva

Legend: RT: radiotherapy; 5-FU: 5-flurouracil; cCR: clinical complete response; MMC: mitomycin-C; CDDP: cisplatin; BLEO: bleomycin; pCR: pathological complete response, CBDCA: carboplatin; AUC: area under curve; PTX: paclitaxel; c.i.: continuous infusion.
[a] All had clinically groin uninvolved nodes; [b]all had unresectable nodes at presentation.

A phase II GOG study included 71 patients with stage III-IV vulvar carcinoma, who received a split course of CDDP/5-FU-based CCRT, followed by surgical excision of the residual primary tumor and inguinal lymphadenectomy [42]. Thirty-one of the 33 clinically complete responders after CCRT underwent surgery, and 22 (71.0%) demonstrated a pathological complete response; 5 patients (16.1%) had microscopic residual disease and negative surgical margins, and 4 (12.9%) had microscopic residual disease with positive surgical margins. In this latter group, 2 patients were salvaged by further excisional surgery. Thirty-three of 38 patients with gross persistent tumor after CCRT underwent surgery, and 28 (84.8%) had negative surgical margins. Of the 5 patients with positive margins, 3 underwent additional RT, one required a wide local excision and vaginectomy with colostomy, and one had no further treatment. Overall, it was not possible to preserve the urinary and/or fecal continence in only 3 cases. After a median follow-up of 50 months, 54.9% of patients were NED.

Gerszten et al. reported of 18 patients with advanced carcinoma of the vulva who received a twice-daily RT schedule delivered with concurrent 5-FU and CDDP, with a complete and partial response in 13 and 5, respectively [44].

In a study published by Gaudineau et al. [46], 22 patients with locally advanced vulvar carcinoma underwent neoadiuvant CCRT with different chemotherapy regimens, followed by radical vulvectomy and inguinal lymphadenectomy. A complete pathological response both in the primary tumor and in the inguinal nodes was reported in 6 patients (27.3%), and in the primary tumor only in 10 patients (45.4%) patients. For the entire cohort, the median OS was 5.1 years.

In a phase II GOG trial, 58 patients with advanced disease received CDDP-based CCRT followed by surgical resection of residual tumor or biopsy to confirm a clinical response [47]. Thirty-seven patients had a clinical complete response at the primary site; among these, 29 had a complete pathological response at surgical biopsy, 5 were found to have persistent vulvar disease and underwent surgical resection, and 3 had inadequate surgical specimen to determine the pathologic response. Therefore, the complete pathological response rates on the primary site among all the evaluable patients and among the clinical complete responders were 50.0% (29/58) and 78.4% (29/37), respectively. Thirty-four women underwent pre-treatment inguinal lymphadenectomy, and 19 out of 34 patients (55.9%) had positive nodes. Twelve patients underwent inguinal lymphadenectomy after CCRT, and 7 of 12 (58.3%) had positive nodes. With a median follow-up of 24.8 months, 31 women were NED (53.4%), 4 were alive with persistent/recurrent tumor (6.9%), 18 died of disease (31.0%), and 5 died of other causes (8.6%).

A meta–analysis of 5 studies of neoadjuvant CCRT [36,38,40,42,45] for advanced primary vulvar carcinoma, reported that the operability was achieved in 63 to 92% of cases treated with 5FU + CDDP or MMC, and only in 20% of those treated with BLEO [48]. After a follow- up ranging from 5 to 125 months, 26% to 63% of women were NED.

In conclusion, all the reported studies confirmed that CCRT can be considered the standard of care in the management of patients with locally advanced vulvar carcinoma who are not deemed eligible for primary surgery, due to unresectable disease or poor PS. The reported clinical complete response rates range from 25.0% to 72.2% [34–47] (Table 2). The decision of whether to proceed with CCRT instead of primary surgery should be taken in a multidisciplinary setting on an individual basis. As noted before, surgery after CCRT is not free of complications. Large and complex resections may be required both at the primary and the inguinal sites, plastic reconstructions may be needed, and surgical healing may be impaired by radiation-induced necrosis and hypoxia.

4.3.2. Role of radiation and chemo-radiation in the neo-adjuvant versus definitive setting

An important clinical question is whether CCRT offers better results compared to RT alone in terms of tumor control and oncologic outcomes, and whether these modalities should be applied before a surgical treatment or as a definitive treatment.

A review of NCDB identified 1352 patients treated with either definitive RT ($n = 353$) or definitive CCRT with different chemotherapeutic agents ($n = 999$), up to a median RT dose of 59.40 Gy [49]. The 5 -year OS was higher in CCRT group than in RT group (49.9% versus 27.4%, $p < 0.001$), and this OS advantage remained significant on multivariate analysis with a HR of 0.76 (95%CI = 0.63–0.91, $p = 0.003$). The benefit of CCRT was found in both patients with positive nodes ($p < 0.001$) and patients with negative nodes ($p < 0.001$) as well as in 75 year-old patients or younger ($p = 0.008$) and older patients ($p = 0.041$).

In another retrospective analysis on 2046 patients included in the NCDB, definitive RT or CCRT was associated with a worse 3-year-OS compared with neoadjuvant RT or CCRT followed by surgery (41.7% versus 57.1%; $p < 0.001$) [50]. However, on multivariate analysis, OS of patients who received definitive RT or CCRT with doses >55 Gy was not significantly different from that of patients who received preoperative RT or CT/RT plus surgery (HR = 1.139; 95% CI = 0.969–1.338; $P = 0.116$). Therefore, with doses >55 Gy, non-surgical approaches seemed to have a clinical outcome comparable to that of RT or CCRT followed by surgery.

Based on these retrospective studies [49,50], CCRT should be considered over RT in the management of patients with locally advanced disease. If a clinical response is achieved, surgery should be considered to obtain the best clinical outcome possible. This approach should be carefully balanced with the risk of severe complications that may affect the individual outcome. Utilization of definitive CCRT is an alternative for fragile patients who are not considered surgical candidates, or in case of pathological confirmed complete response.

In this perspective, the NCT01595061 is an ongoing phase II trial designed to assess the efficacy of primary concurrent CDDP and gemcitabine-based CCRT with IMRT in achieving a pathological complete response in stage III-IV squamous cell carcinoma of the vulva.

4.3.3. Management of the groin disease

Another challenging question is represented by the management of patients with grossly involved nodes. These are usually treated with radical groin lymphadenectomy and adjuvant RT. This approach is associated with a high incidence of wound dehiscence or infection, severe lymphedema, and lymphocyst formation. For these reasons, the utilization of CCRT as a definitive treatment or prior to a surgical approach has been studied as a possible alternative.

Montana et al. [45] reported of 46 patients with unresectable groin nodes, who received a split course of CCRT to the primary tumor and to the inguinal nodes (Table2). Of the 38 patients who completed the scheduled treatment, 37 underwent inguinal lymphadenectomy and resection or biopsy of the primary tumor, and one patient underwent resection of the primary tumor only. The histologic examination showed a pathological complete nodal response in 15 of the 37 patients (40.5%) who underwent lymphadenectomy, whereas the surgical specimen of the primary tumor was negative in 20 of the 38 patients (52.6%). After a median follow-up of 78 months, 12 patients (31.6%) were NED, 5 patients (13.2%) died of intercurrent disease, 2 (5.2%) died of treatment-related complications, and 19 (50.0%) relapsed. Of these, 9 had a local recurrence only, 8 had a distant recurrence, one patient had a local and distant recurrence, and the last patient had a nodal recurrence. Therefore, the scheduled CCRT obtained a high resectability rate, and an excellent nodal control rate (36/37, 97.3%) in patients with unresectable groin metastases at presentation.

Stecklein et al. [32] reviewed a cohort of 33 patients who received definitive RT, using 3D-CRT, IMRT or a combination of both, for grossly involved groin nodes, treated at MD Anderson Cancer Center between 1992 and 2014. All patients received an initial dose of 40 to 50 Gy of external beam RT to the vulva (primary tumor), bilaterally to the inguinal regions, and to the pelvis. Different techniques were subsequently employed to reach a total dose of at least 60 Gy to all sites of grossly involved disease. Twenty patients also received concurrent CDDP (40 mg/m^2 per week) or a combination of CDDP and 5-FU. The 3-year rates of vulvar, groin, and distant recurrences were 24.2%, 17.7%, and 30.3%, respectively, with a 3-year OS for the entire cohort of 51%. Only three major long-term adverse events were recorded. According to the authors, the decision of whether to treat these patients with definitive groin CCRT versus surgery followed by adjuvant RT should be made on several factors, including the size, number, location of the involved nodes, and patient's body habitus. For instance, thin patients with enlarged nodes close to the skin surface are more likely candidates for surgery, although the morbidity and potential for adjuvant treatment delays following an extensive lymphadenectomy must be taken into account in the decision making process. Conversely, definitive CCRT should be preferred in patients with concomitant massive unresectable vulvar tumors, since the ability to control local disease usually dominates patient prognosis, and the resection of enlarged nodes is unlikely to improve the clinical outcome. These different options in treating nodal disease should be carefully evaluated on an individual basis by a multidisciplinary, expert team in treating this challenging disease.

4.4. Neoadjuvant chemotherapy

The role of neoadjuvant chemotherapy in the management of locally advanced vulvar carcinoma has been recently studied, but the available results reported in the literature are limited [51–54] (Table 3). Potential benefits of such approach reside mainly in the possibility to avoid the morbidity of exenterative procedures or CCRT followed by surgery, and to potentially control for subclinical distant metastases.

In a European Organization for Research and Treatment of Cancer (EORTC) study, the combination of BLEO + lomustine (CCNU) + methotrexate (MTX) achieved 2 complete responses and 12 partial responses among 25 patients with locally advanced or recurrent squamous cell carcinoma of the vulva, with an overall response rate of 56.0% [51]. This treatment was associated with major hematological toxicities and mild signs of BLEO-related lung toxicity. Surgery was attempted in 8 of the 14 responding patients, resulting in complete excision of the tumor with free margins in 4 of them. The other 4 patients had positive surgical margins or unresectable groin nodes and underwent definitive RT. In the entire cohort, the median PFS was 4.8 months, the median OS was 7.8 months, and the 1-year OS was 32%.

Benedetti-Panici et al. [52] analyzed the clinical outcome of 21 patients with advanced squamous cell carcinoma of the vulva treated with a neo-adjuvant combination of CDDP+ BLEO+ MTX. This approach obtained a partial response in the primary tumor in 2 patients (9.5%), and a complete response and a partial response in the groin nodes in 11 (52.4%) and 3 patients (14.3%), respectively. Nineteen (90.5%) patients underwent surgery, and final pathology demonstrated persistent disease in the groin and pelvic nodes in 81% and 47%, respectively. Sixty-eight percent of the operated patients recurred after a time ranging from 3 to 17 months, with a 3-year OS of 24%.

In the retrospective investigation reported by Geisler et al., 13 patients with locally advanced vulvar carcinoma involving the anal sphincter and/or the urethra underwent neoadjuvant chemotherapy with CDDP +5-FU (N:10), or single-agent CDDP (N:3), in the attempt to preserve these viscera [53]. All patients treated with CDDP +5-FU had an objective clinical response. They underwent radical vulvectomy and inguinal lymphadenectomy with preservation of the anal sphincter and the urethra, except of one patient who died before surgery for a synchronous renal cell carcinoma. All these 10 patients were NED at the time of publication. Conversely, none of the 3 patients receiving CDDP alone obtained a clinical objective response. One received definitive RT, and two underwent palliative radical vulvectomy, followed by RT. All the 3 patients eventually died of their disease.

Raspagliesi et al. [54] reported on the use of neoadjuvant paclitaxel [PTX] + ifosfamide [IFO] + CDDP or PTX + CDDP in 10 patients with stage III-IV squamous cell carcinoma of the vulva. Nine patients subsequently underwent individualized radical surgery and inguinal lymphadenectomy. Pathological examination revealed a complete response in one patient (11.1%), persistent in situ carcinoma in 2 patients (22.2%), and invasive carcinoma with tumor shrinkage >50% in 6 patients (66.7%). Positive nodes and positive surgical margins were found in 4 (44.4%) and 3 (33.3%) cases, respectively. Seven of the 9 operated patients (77.8%) relapsed, and 6 of them had local recurrences. After a median follow-up of 40 months, 5 patients were NED, 4 patients died of tumor, and one was alive with a recto-anal carcinoma diagnosed 46 months after surgery.

Table 3
Neoadjuvant chemotherapy in advanced squamous cell carcinoma of the vulva.

Authors [ref]	Drug	Patients	Clinical response	
Wagenaar [51]	BLEO 5 mg im d 1–5 week 1 CCNU 40 mg po d 5–7 week 1 MTX 15 mg po d 1,4 week 1 BLEO 5 mg im d 1,4 weeks 2–6 MTX 15 mg po d 1 weeks 2–6 repeated at 49-day intervals up to 3 cycles	25	CR = 2 (8.0%)	PR = 12 (48.0%)
			Primary	Groins
BenedettiPanici [52]	CDDP 100 mg/m^2 d1 BLEO 15 mg d 1, 8 MTX 300 mg/m^2 d 8 repeated at 21-day intervals for 2–3 cycles	21	PR = 2 (9.5%)	CR = 11 (52.4%) PR = 3 (14.3%)
Geisler [53]	CDDP 50 mg/m^2 d1 + 5-FU 1000 mg/m^2 / c.i. d 1–5	10	CR = 1 (10%)	PR = 9 (90%)
	CDDP 50 mg/m^2 d1 repeated at 21-day intervals for 3–4 cycles	3	0	0
Raspagliesi [54]	PTX 175 mg/m^2 day 1 + CDDP 50 mg/m^2 day 1 + IFO 5 g/m^2 24-h c.i. d2	4	CR = 1 (25.0%)	PR = 3 (75.0%)
	PTX 175 mg/m^2 d1 + CDDP 70 mg/m^2 day 1 repeated at 21-day intervals for 3 cycles	6	CR = 2 (33.3%)	PR = 2 (33.3%)
		Overall 10	3 (30.0%)	5 (50.0%)

CDDP alone or combination with 5-FU was chosen by staff physician.
Legend: BLEO: bleomycin; CR: complete response; PR: partial response; CCNU: lomustine; MTX: methotrexate; CDDP: cisplatin; 5-FU: 5-flurouracil; PTX: paclitaxel; IFO: Ifosfamide; c.i.: continuous infusion.

In a prospective multicenter study published by Aragona et al., 33 patients with locally advanced squamous cell carcinoma of the vulva completed neoadjuvant chemotherapy with 4 different CDDP-based regimens or with single-agent BLEO, followed by radical surgery and inguinal lymphadenectomy, if the clinical response was superior to 50% [55]. Twenty-seven patients underwent radical surgery, including 2 posterior pelvic exenterations for persistent rectal involvement. Twenty-four patients (88.9%) were NED after a median follow-up of 49 months.

We must consider that the reported studies have not adequately assessed the combination of PTX + platinum with or without bevacizumab, which constitute the most used agents in gynecologic malignancies. This protocol was assessed in a small case series of 3 patients published by Amant et al., showing promising results [56]. The potential role of the immune checkpoint inhibitors has been recently evaluated by analyzing the expression of PD-L1, PD-1 and CD8 by immuno-histochemistry [57]. The phase I/II CheckMate 358 trial showed a promising efficacy of nivolumab in patients with recurrent/metastatic cervical, vaginal or vulvar cancers [58].

Considering the overall results of neoadjuvant chemotherapy, this approach should be considered still investigational in patients with locally advanced vulvar carcinoma both for the limited results, and for the difficulties to deliver such aggressive drug regimens in old women often burdened with severe comorbidities. However, considering the potential benefits in terms of resectability and treatment-related morbidity, studies that investigate the role of neo-adjuvant chemotherapy or the role of biological agents in this clinical scenario are warranted.

5. Discussion

According to the FIGO 26th Annual Report, the 5-year OS rates for 1988 FIGO stage III and IV vulvar carcinomas are 43.3% and 13.0%, respectively [16].

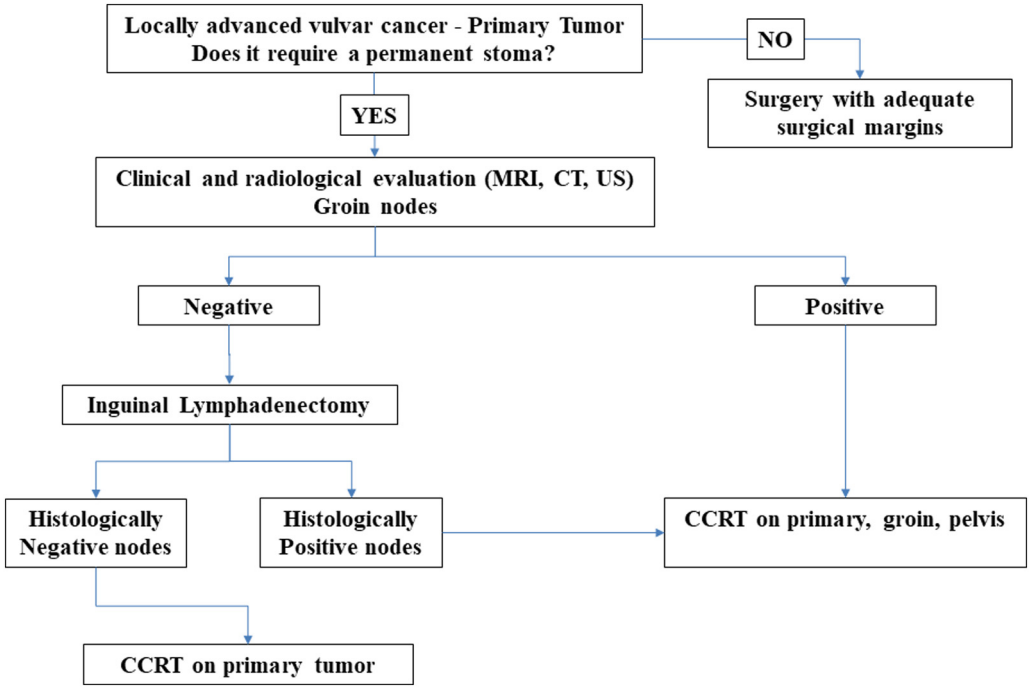

Fig. 1. Algorithm of treatment of locally advanced squamous cell carcinoma of the vulva.

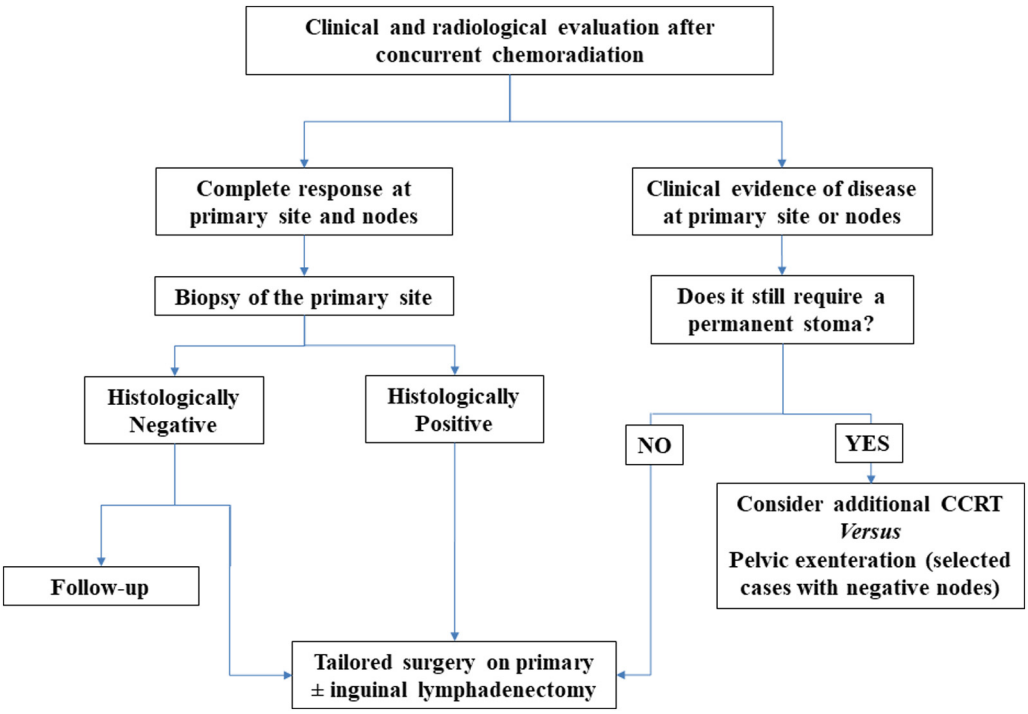

Fig. 2. Algorithm of evaluation/treatment of locally advanced squamous cell carcinoma of the vulva after concurrent chemo-radiation.

CT scan or MRI is recommended in these patients to detect any enlarged nodes in the groins or pelvis and to assess the relationship with surrounding organs. Cistoscopy and/or rectoscopy should be reserved to patients with suspicious urethra, bladder or rectal involvement. Positron emission tomography (PET/CT) should be performed in patients with pelvic nodal or distant metastases suspected at CT or MRI [59]. The surgical treatment for such advanced cases often requires exenterative procedures, with the formation of a bowel or urinary stoma. This approach carries an impressive morbidity, with a high incidence of failure, even in properly selected cases. Moreover, no long-term survivors are reported among patients with positive nodes [24,26,28]. Therefore, the approach to patients with locally advanced disease remains a clinical dilemma, especially if we consider that these patients are often old with many age-associated comorbidities.

For these reasons, this review aimed in developing a clinical algorithm that may help physicians who treat these challenging patients (Figs. 1 and 2). A careful pre-treatment evaluation of the primary site, the inguinal areas, and the presence of pelvic or distant metastases should be done, in order to define the proper management.

Regarding the primary site, upfront radical surgery should be considered when it is possible to remove the tumor with adequate surgical margins without sphincter damage and without need for a bowel or urinary stoma. CCRT should be regarded as the first choice for patients with large tumors, in whom primary surgical resection would require a bowel and/or a urinary diversion [48,60] (Fig. 1). This treatment modality can reduce the tumor size and improve operability rates, with individualized surgical approaches. Unfortunately, wound breakdown, infection, necrosis, lymphedema, and lymphocele are very common side effects of these combined strategies**.** For these reasons, a radical exenterative procedure may be considered as a first option in selected cases. CCRT can also be used as definitive treatment in case of a complete pathologic response demonstrated at post-treatment biopsy (Fig. 2). Although the choice of the best CCRT regimen with the least toxicity is difficult due to small study populations and to the heterogeneity of the inclusion criteria in the different studies, weekly CDDP or a combination of CDDP and 5-FU are the most commonly used agents. The total RT dose recommended by Thomas et al. [9] is approximately 55 Gy for preoperative CCRT and 65 Gy for definitive CCRT. The clinical complete response rates following CCRT range from 25.0.% to 72.2% [34–47]. However, disease subsequently relapses in up to one third of the complete responders.

Regarding the inguinal nodes, CCRT to the groin and the pelvic area should be administered for clinical and/or pathological positive nodes. Only in case of pathologically proven negative nodes this approach can be spared. Another option in clinically negative nodes by imaging techniques (CT or PET/CT), would be to avoid the full inguino-femoral lymphadenectomy, and include the inguinal regions in the irradiated field (Fig. 1). After CCRT, a systematic inguino-femoral lymphadenectomy should be taken in consideration (if not performed primarily) in case of positive nodes at presentation with a significant clinical response also at the primary site (Fig. 2).

Prospective multicenter collaborative studies comparing different treatment modalities (including neo-adjuvant chemotherapy +/− biological agents) and new therapeutic biological agents, are strongly warranted in patients with locally advanced squamous cell carcinoma of the vulva [21,60]. Besides recurrence rate, PFS and OS, these trials should adequately investigate the psychosexual sequelae, body image disfigurement, the impact of eventual stoma formation, and the overall quality of life.

Author contribution

AG and GDA equally contributed to the manuscript.

Authors' roles

Angiolo Gadducci: Conceptualization, methodology, data extraction and analysis, writing (original draft - review & editing).

Giovanni Aletti: Methodology, data extraction and analysis, writing (original draft - review & editing).

Declaration of competing interest

The authors declare no conflict of interest.

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