Neoadjuvant chemotherapy for patients with locally advanced vulvar cancer

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Purpose of review
Studies on treatment options for patients with locally advanced vulvar cancer (LAVC) are scarce, and high-level evidence for a primary treatment choice is lacking. Furthermore, current treatment options are associated with extensive morbidity and high complication rates. More effective treatment options are urgently needed. This review describes current treatment possibilities, focusing on literature regarding neoadjuvant chemotherapy (NACT) followed by surgery.

Recent findings
Although data are heterogeneous and limited, NACT followed by surgery might be an effective and well tolerated treatment alternative associated with lower morbidity compared with current treatment options, such as excenterative surgery or definitive chemoradiation.

Summary
Up until now, several studies describe an overall response rate of 40–86%. Surgery turned out to be possible in 40–90% of the LAVC patients who received NACT. Prospective studies on the efficacy and safety of NACT followed by surgery with a homogeneous chemotherapy regimen are urgently awaited. NACT should, at this point, still be considered investigational.

Keywords
definitive chemoradiation, locally advanced vulvar cancer, neoadjuvant chemotherapy followed by surgery

INTRODUCTION

Vulvar cancer accounts for 3–5% of all gynaecological malignancies [1,2] and has an incidence rate of two to three newly diagnosed patients per 100 000 women per year [3]. Prognosis strongly depends on the stage at diagnosis. Patients with early-stage disease have an excellent 5-year survival of 80–90% [4,5], but this decreases to 25–67% if patients have tumour-positive groin lymph nodes [6]. The peak incidence of vulvar cancer is between 60 and 70 years of age, which makes this patient group often frail with a high chance on comorbidities. Surgery is the cornerstone of treatment for vulvar cancer [5]. During the last decades, treatment for vulvar cancer has evolved into an individualized approach in which the characteristics of the primary tumour determine the extent of surgery needed [5,7]. For most early-stage vulvar cancer patients, surgical treatment consists of radical local excision of the primary tumour combined with a sentinel node procedure of the groins or bilateral inguinofemoral lymphadenectomy depending on tumour characteristics [5,8].

Around 10–30% of vulvar cancer patients present with locally advanced vulvar cancer (LAVC) [9–11]. The definition of LAVC holds different entities and includes a large primary tumour extending beyond the vulva, a tumour close to or involving surrounding organs (vagina, urethra, bladder, anus and/or rectum) or a tumour fixed to the pelvic bones. In addition, LAVC can refer to a patient with extensive lymphadenopathy in the groin(s). Basically, LAVC refers to vulvar cancer patients for whom standard radical vulvar resection and bilateral inguinofemoral lymphadenectomy is not a surgical treatment option [12–14]. Treatment options for LAVC are less standardized resulting in a more individualized approach after extensive discussions

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KEY POINTS

- Treatment for locally advanced vulvar cancer patients is individualized and should be discussed in a multidisciplinary setting.
- At this moment, definitive chemoradiation can be considered as the first treatment of choice for locally advanced vulvar cancer patients.
- Neoadjuvant chemotherapy followed by surgery might be an effective and well tolerated treatment alternative in this frail patient population.

in a multidisciplinary setting. Treatment options can consist of an extensive surgical procedure; partial or complete exenteration, neoadjuvant or definitive radiotherapy, neoadjuvant or definitive chemoradiation or neoadjuvant chemotherapy (NACT) followed by surgery (Fig. 1) [11,13]. Depending on treatment results, adjuvant treatment might be necessary. As there is no standard treatment option that fits all LAVC patients, multimodal clinical approaches are necessary. In the absence of randomized trials, expert opinion and small observational studies are the basis for the decision-making process. In some patients (especially in frail patients), no treatment can also be an option. For these patients, best supportive care is advised.

This review gives an overview on the current treatment options for patients with LAVC focusing on NACT followed by surgery as an interesting alternative treatment approach. An overview of the literature published so far and the clinical challenges of NACT followed by surgery for this population are described.

CURRENT TREATMENT OPTIONS FOR LOCALLY ADVANCED VULVAR CANCER PATIENTS

Evidence for the different treatment strategies is scarce due to the rarity of this disease and resulting challenges to conduct prospective studies. Surgical treatment consisting of a partial or total exenteration of the pelvis is often the only surgical treatment option that can completely remove the primary tumour in patients with LAVC. This extensive surgery includes the construction of a permanent urostoma, colostoma or both. Because of the extend of exenterative surgery, this surgery is associated with high morbidity rates and a peri-operative mortality rate of up to 2% [10,15,16]. Furthermore, patients often develop psychological problems due to major alterations in body image and loss of sexual function [8].

An alternative treatment option is radiotherapy alone or combined with surgery or treatment with neoadjuvant chemoradiation. Data on radiotherapy alone as a treatment option are difficult to interpret, because in most studies, a large proportion of patients received concomitant chemotherapy. A recent retrospective chart study on the clinical outcomes of 26 LAVC patients treated with high-dose intensity modulated radiation therapy (IMRT) showed a complete clinical response in 80.7% of the patients. However, concurrent platinum-based chemotherapy was given to 22 patients (84.6%). Five patients (19.3%) experienced grade 3-4 late urinary and soft tissue toxicity [17]. A large cohort study on the use of primary (chemo)radiotherapy compared with (chemo)radiotherapy followed by surgery in 2046 LAVC patients showed that primary (chemo)radiotherapy let to a compromised overall survival (OS) compared with (chemo)radiotherapy followed by surgery (41.7 versus 57.1% after 3 years, $P < 0.001$). A [18]. Neoadjuvant chemoradiation has been studied in several case series (number of patients 9–71). Most patients were treated with 5-fluorouracil and mitomicin C or cisplatinum combined with radiotherapy. A complete clinical response was established in 25–72% of the patients. The number of patients who underwent subsequent surgical treatment differed greatly in the published studies, between 20 and 100% of the patients. Complete pathological response was seen in 28.6–100% of the patients [3,19–32].

Definitive chemoradiation has emerged as an alternative organ-sparing treatment option in the past years [19,33]. At this moment, the National Comprehensive Cancer Network recommends chemoradiation with or without inguinofemoral lymphadenectomy as treatment of choice for LAVC patients [4]. However, evidence for the efficacy of this treatment strategy is relatively limited. Most studies on definitive chemoradiation are retrospective and present heterogeneous treatment regimens making conclusions on efficacy of these treatments difficult [19,34]. Within a recent multicentre prospective phase II study, 52 LAVC patients were treated with locoregional radiotherapy combined with capecitabine (825 mg/m^2 twice daily during days 1–14, 22–35 and 43–49 of treatment). Twelve weeks after treatment, local clinical complete response and regional control rates were 62 and 75%, respectively. Thirty patients (58%) had no evidence of disease at the end of follow-up (median 35 months). In nine patients (17%), extensive surgery with stoma formation was needed (five urostoma and four colostoma). Most prevalent acute at least grade 3 toxicities considered skin/mucosa and pain (54 and 37%). Late at least grade 3 toxicity regarded skin/mucosa (10%), fibrosis

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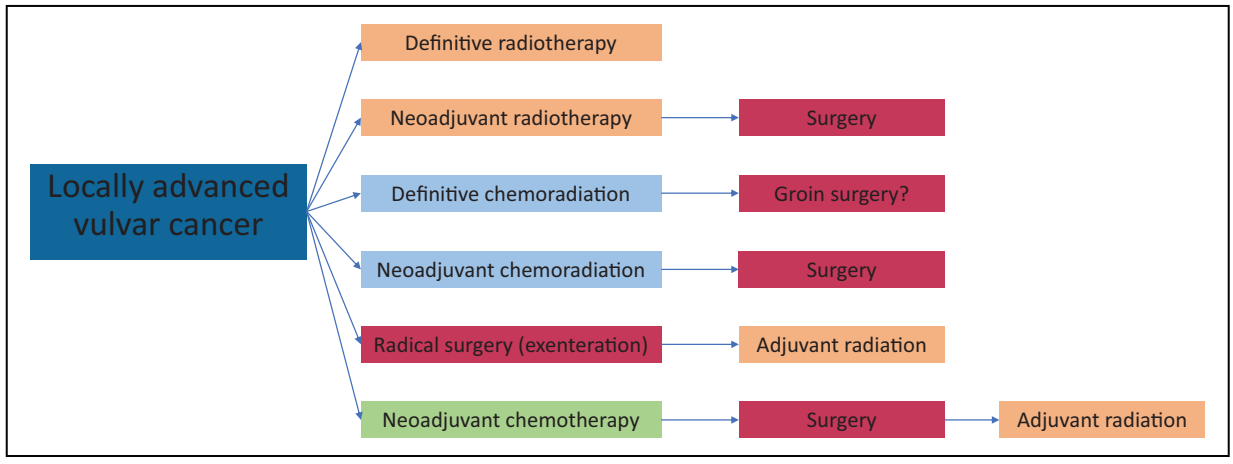

FIGURE 1. Overview of current treatment options for patients with locally advanced vulvar cancer.

(4%), gastrointestinal incontinence (4%) and stress fracture or osteoradionecrosis (4%). On the basis of these data, it appears that capecitabine-based chemoradiation is feasible in LAVC patients and not only results in considerable locoregional control but also in high morbidity rates [35▪].

A major disadvantage of chemoradiation, in general, is that it limits future treatment options (such as salvage radiotherapy) in case of recurrent disease [36].

Chemotherapy, and especially NACT, followed by surgery might be a good treatment alternative for the treatment of LAVC patients. At this moment, chemotherapy is primarily considered as a palliative treatment option in the treatment of vulvar cancer patients. Research on the effectiveness and safety of chemotherapy as a curative treatment option is difficult due to the low incidence of LAVC patients who possibly benefit from treatment with chemotherapy, especially in the neoadjuvant setting. The next paragraph focusses on the clinical challenges of treatment with NACT followed by surgery in patients with LAVC. After that, an overview on the current literature is given.

CHALLENGES OF TREATMENT WITH NEOADJUVANT CHEMOTHERAPY FOLLOWED BY SURGERY IN LOCALLY ADVANCED VULVAR CANCER PATIENTS

Although NACT can be considered as a valuable novel treatment strategy in LAVC patients, there are several important (clinical) challenges that should be addressed.

Rarity of the tumour

One of the major challenges is that data on the safety and effectiveness of NACT in LAVC patients remain scarce as described in the previous paragraph. It is difficult to perform a prospective or randomized clinical trial that can demonstrate which chemotherapy regimen is most effective with the least side effects due to the fact that LAVC falls into the rare tumour category.

Heterogeneity of neoadjuvant chemotherapy treatment strategies

Currently, chemotherapy treatment protocols used in the available studies are heterogeneous, which makes it very hard to draw definite conclusions on the effectiveness of NACT as a treatment option for LAVC patients and especially on which treatment strategy is most optimal. Because of the effectiveness of three-weekly carboplatin combined with paclitaxel in other gynaecological malignancies and in the palliative treatment setting of vulvar cancer patients [37–39], this treatment strategy might be valuable for LAVC patients as well. At this moment, treatment with NACT followed by surgery should still be considered investigational in LAVC patients, especially because definitive chemoradiation is an effective treatment alternative. However, concerns about the toxicity associated with potential trimodal treatment exist, certainly in an older and frailer patient population. This toxicity can best be tested in prospective studies.

Treatment of the groin(s)

Another important challenge when treatment with NACT is considered in LAVC patients, is the treatment of the groin(s). When a vulvar cancer patient presents at the outpatient clinic, it is essential to start treatment soon. In a small subset

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of LAVC patients, there might be a role for a sentinel node procedure prior to the start of chemotherapy. In case of a negative sentinel node, further inguinal treatment can be avoided. Decisions on a positive sentinel node should be done on individual basis. However, most LAVC patients will present with tumours larger than 4 cm, which makes them ineligible for a sentinel node procedure. Furthermore, patients with LAVC will have a high chance of metastasis to the lymph nodes in the groin(s). Due to the current uncertainty on effectiveness of chemotherapy in vulvar cancer, it is conceivable to start the treatment of the patient with an inguinofemoral lymphadenectomy. A major disadvantage of this strategy is that the start of the chemotherapy has to be postponed until the patient has recovered from her first surgery, including a potential delay due to inguinal complications, while the local tumour will have a chance of further growth. In addition, patients require two surgical procedures instead of one combined surgery. Another option could be to start with chemotherapy and closely evaluate the effect of the chemotherapy on possible lymph node metastases. At this moment, the effect of chemotherapy on inguinal node metastases and the possibility of progressive disease during treatment with chemotherapy is unknown. After NACT, surgery of the local tumour can then be combined with surgery of the groin(s). The next issue is whether or not patients should receive adjuvant radiotherapy after surgery. It is arguable that patients only require adjuvant radiotherapy when there are still lymph node metastases present in the groin(s) during resection, irrespective of the number or size of the metastases initially. Probably, patients without lymph node involvement after chemotherapy can be denied further radiotherapy.

Thus, NACT followed by surgery might be a reliable and promising therapeutic option, hopefully leading to less treatment-related morbidity. Studies on the effectiveness and safety of NACT in LAVC are urgently needed. These studies should not only determine the safety and effectiveness of NACT but also which treatment regimen and which LAVC patients will benefit most from treatment with NACT. It is highly important that the chemotherapy treatment regimen used within clinical studies becomes more homogeneous. In that way, it will become more feasible for researchers and clinicians to collect valuable research data in this rare patient group. In the next paragraph, the literature published thus far on NACT for LAVC patients is described.

CURRENT EVIDENCE FOR TREATMENT WITH NEOADJUVANT CHEMOTHERAPY FOLLOWED BY SURGERY FOR LOCALLY ADVANCED VULVAR CANCER PATIENTS

NACT followed by surgery is a common treatment option in other gynaecological cancers. The goal of NACT is to reduce tumour size, thereby facilitating subsequent surgical treatment. The treatment regimen consisting of a combination of paclitaxel and carboplatin has proven to be successful in ovarian cancer and endometrial cancer patients with initial bulky disease [37–41]. Nowadays, NACT with 3-weekly carboplatin and paclitaxel has become standard of care in advanced-stage ovarian cancer patients not eligible for primary cytoreductive surgery [38,39]. Furthermore, treatment with paclitaxel and carboplatin is standard of care in the palliative treatment setting for vulvar cancer patients.

NACT for LAVC patients has been investigated in several case series. Between 2019 and 2021, one cohort study and one case report on the use of NACT in LAVC patients were published.

In 2021, Marco *et al.* [42▪▪] reported a retrospective study on 15 LAVC patients treated with NACT followed by surgery. Chemotherapy was platinum-based and consisted of a combination of paclitaxel-ifosfamide-cisplatin, paclitaxel-cisplatin or paclitaxel-carboplatin and was administered in a three-weekly schedule. The median number of chemotherapy cycles was 3 (with a range of 2–6). After completion of chemotherapy, patients were clinically and radiologically evaluated, and adjuvant treatment was then discussed in a multidisciplinary meeting. Fourteen patients (93%) completed chemotherapy. Thirteen patients (87%) underwent surgical treatment, consisting of a radical vulvectomy combined with inguinofemoral lymphadenectomy in 11 patients. In two patients, surgical treatment of the groin(s) was omitted. This was due to severe comorbidity in one patient and due to advanced-stage disease in the other patient. The overall response of the vulvar tumour on NACT was 66% (20% complete response and 46% partial response). The overall inguinal lymph node response was 69% (23% complete response and 46% partial response). There were no severe postoperative complications. Five-year survival was 60% [42▪▪].

Klavans *et al.* [43▪▪] described the treatment of two LAVC patients with irresectable vulvar tumours with NACT consisting of paclitaxel, carboplatin and bevacizumab. Due to the stage of their disease (one patient with stage IVB and one patient with stage IVA), chemotherapy was started. In both patients, there was a spectacular decrease in the size of the vulvar tumour mass after which they were able to stop their pain medication. Due to this spectacular

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Table 1. Previous studies on neoadjuvant chemotherapy in locally advanced vulvar cancer

Ref.	Number of patients	Chemotherapy regimen	Number of patients who underwent surgery	Clinical response	Pathological response	Adjuvant therapy	Survival
Domingues *et al.* [44], retrospective	25	Bleomycin or paclitaxel or 5-fluorouracil/cisplatin	40% (10/25)	ORR 40% (10/25) (1 CR, 9 PR)	Not described	Not described	Mean OS 22.8 months
Aragona *et al.* [9], prospective	35	Cisplatin/5-fluorouracil or cisplatin/paclitaxel or cisplatin/paclitaxel/5-fluorouracil or vincristine/bleomycin/cisplatin or bleomycin	77,1% (27/35)	ORR 86% (30/35) (30 PR), SD 8.6% (3/35)	29,6% (8/27) CR	Not described	Not described
Han *et al.* [47], retrospective	4	Carboplatin/paclitaxel	50% (2/4)	ORR 0%	Not described	Not described	Median 4.2 months
Raspagliesie *et al.* [32], prospective	10	Paclitaxel/ifosfamide/cisplatin or paclitaxel/cisplatin	90% (9/10)	ORR 80% (8/10) (3 CR, 5 PR), SD 10% (1/10), PD 10% (1/10)	10% CR, 20% PR	1/10 (10%) CT, 4/10 (40%) RT	Median PFS 14 months
Niu *et al.* [14] retrospective	12	Bleomycin, cisplatin, ±vincristine or carboplatin - paclitaxel	75% (9/12)	ORR 67% (8/12), SD 17% (2/12), PD 17% 2/12	Not described	2/12 (17%) CT+RT, 3/12 (25%) CT	Mean OS 28.5 months
Amant *et al.* [33], retrospective	2	Carboplatin/paclitaxel	100% (2/2)	ORR 100% (2/2) (2 PR)	100% PR	None	Not described
Klavans *et al.* [43▪▪], retrospective	2	Carboplatin/paclitaxel/bevacizumab	0% (0/2)	ORR 100% (2/2) (2 CR)	Not available	Bevacizumab	Not described
Marco *et al.* [42▪▪], retrospective	15	Paclitaxel/ifosfamide/cisplatin or paclitaxel/cisplatin or paclitaxel/carboplatin	87% (13/15)	ORR 66% (3 CR, 7 PR)	Not described	3/15 (20%) RT, 4/15 (26,7%) CRT	Median OS 76 months

CR, complete response; CT, chemotherapy; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; RT, radiotherapy; SD, stable disease.

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response, surgical treatment was omitted. Currently, both patients receive maintenance therapy with bevacizumab [43▪▪].

Between 2010 and 2019, six case series on the use of NACT followed by surgery for LAVC were published [9,14,44–47]. A summary of these studies and the studies of Marco *et al.* [42▪▪] and Klavans *et al.* [43▪▪] are presented in Table 1. The number of LAVC patients who were included in these studies varied from 3 to 35. Chemotherapy regimens used in these studies were heterogeneous and consisted of several combinations of chemotherapy, also within the individual studies. Overall response rate was 40–86%. Surgery turned out to be possible in 40–90% of the LAVC patients who received NACT [9,14,42▪▪,43▪▪,44–47].

Older case series that included more than 10 patients describe a response rate ranging from 58 to 90%. Again, chemotherapeutic regimens were highly heterogeneous. Chemotherapeutic agents used in these case series were bleomycin, methotrexaat, lomustine and cisplatin in various combinations [3,13].

FUTURE OPPORTUNITIES

Additional to further studies on the benefits of NACT for the treatment of LAVC patients, future opportunities comprise the use of targeted therapies. In the last few years, targeted therapies have high clinical and scientific interests. At this moment, little is known about genetic and molecular alterations in vulvar cancer [48–50]. Further knowledge on the underlying molecular pathogenesis of vulvar cancer can support the use of certain targeted therapies. Therapeutic targets of interest for the treatment of vulvar cancer has thus far focused on the epidermal growth factor receptor (EGFR) signalling cascade and on vascular endothelial growth factor (VEGF) as described in the study of Klavans *et al.* [43▪▪] in the previous paragraph. Anti-EGFR and anti-VEGF have been used as targeted therapy in patients with cervical cancer or head and neck cancer, which are both cancer types with a comparable pathogenesis to vulvar cancer [13,50].

Another type of therapy that has been suggested for the treatment of vulvar cancer is immune therapy with a humanized mAb against programmed death (PD-1), for example pembrolizumab. The use of pembrolizumab has dramatically altered the oncology scene. However, only few case reports have been published that also describe a clinical response to pembrolizumab in LAVC patients with mutations in PD-L1 and PD-1 [51,52]. In the near future, a single-arm phase II clinical trial will start for patients with irresectable, locally advanced or metastatic vulvar cancer on pembrolizumab combined with chemoradiation [53].

A completely different, but interesting type of therapy is treatment of LAVC with electrochemotherapy as primary treatment or combined with other treatment options. With this therapy, the patient will receive electric pulses in the primary tumour in order to achieve transient tumour permeabilization. These electric pulses are combined with low-dose chemotherapy. Few patients have been treated with electrochemotherapy in a palliative treatment setting. Response rates varied from 30 to 62%. No severe adverse events have been reported [54].

Of course, more research on all of these types of treatment is necessary, but future possibilities for LAVC patients seem promising.

CONCLUSION

Treatment of LAVC patients remains challenging due to the currently available treatment options that are all associated with a high risk of morbidity. This, in a largely frail patient population, results in a challenging decision-making process. Indeed, these treatment options all lead to major side effects and disadvantages. It is therefore utterly important to discuss and treat all LAVC in a multidisciplinary setting in a specialized oncologic treatment centre. Patients should be adequately informed about all possible treatment options and the benefits and drawbacks of all of these treatments. In that way, it is possible to present each patient a well considered, individualized treatment plan. The use of NACT followed by surgery is a potentially successful strategy that needs further investigation. Ideally, future decisions in this matter are based on prospective, well designed clinical studies or at least all clinicians should guarantee careful registration of all LAVC patients treated with NACT followed by surgery.

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Conflicts of interest

There are no conflicts of interest.

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- ▪ of special interest
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