Primary chemoradiation versus neoadjuvant chemotherapy followed by surgery as treatment strategy for locally advanced vulvar carcinoma (VULCANize2)

Amant, F.; Velzen, A.F. van; Reyners, A.; Zijlmans, H.; Schaake, E.E.; Nooij, L.

Primary chemoradiation versus neoadjuvant chemotherapy followed by surgery as treatment strategy for locally advanced vulvar carcinoma (VULCANize2)

Frédéric Amant ,[1,2] Anne Fleur van Velzen ,[2,3] An Reyners,[4] Henry Zijlmans,[2] Eva E Schaake,[5] Linda Nooij [3]

For numbered affiliations see end of article.

Correspondence to
Professor Frédéric Amant, Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University Hospitals Leuven, Katholieke Universiteit Leuven, Herestraat 49, 3000, Leuven, Belgium; frederic.amant@uzleuven.be

EES and LN contributed equally.

Accepted 16 April 2024

To cite: Amant F, van Velzen AF, Reyners A, *et al*. *Int J Gynecol Cancer* Published Online First: [please include Day Month Year]. doi:10.1136/ijgc-2024-005493

ABSTRACT

Background Current treatment options for patients with locally advanced vulvar cancer are limited and associated with high morbidity. Therefore, it is important to develop new and safe treatment strategies for this vulnerable patient group.

Primary Objective To compare the efficacy and safety of neoadjuvant chemotherapy followed by surgery with definitive chemoradiation in patients with locally advanced vulvar cancer.

Study Hypothesis Neoadjuvant chemotherapy followed by surgery is oncologically safe, potentially more effective than primary chemoradiation in establishing long lasting locoregional control, and associated with an improved quality of life.

Trial Design This study is a multicenter, prospective, phase II randomized controlled trial. Patients will be randomized 1:1 to the standard treatment arm (primary chemoradiation, consisting of a tumor dose of 64.5 Gy in 30 fractions of external beam radiotherapy with weekly cisplatin for 6 weeks) or the experimental treatment arm (neoadjuvant chemotherapy, consisting of carboplatin and paclitaxel in a 3 weekly scheme, followed by surgery).

Major Inclusion/Exclusion Criteria Eligible patients must have a histologically confirmed primary or recurrent locally advanced squamous cell carcinoma of the vulva (International Federation of Gynecology and Obstetrics (FIGO) stages Ib–IVa; Lesions larger than 2 cm in size or stromal invasion larger than 1 mm (T1b or higher), any status of lymph node involvement (any N), no distant metastasis including pelvic lymph nodes (M0)) with the size or localization of the tumor requiring treatment through primary chemoradiation or extensive surgery. Patients with documented metastases of the pelvic lymph nodes will be excluded from participation in this study.

Primary Endpoint Locoregional control at 24 months.

Sample Size 98 patients will be included in the study.

Estimated Dates for Completing Accrual and Presenting Results Expected complete accrual in 2028 with presentation of results by 2030.

Trial Registration ClinicalTrials.gov NCT05905315

INTRODUCTION

About one-third of all patients with vulvar cancer present with locally advanced disease.[1 2] The definition of locally advanced vulvar cancer involves different entities. These entities include a large primary tumor extending beyond the vulva, a tumor close to or involving surrounding organs (vagina, urethra, bladder, anus, and/or rectum), or a tumor fixated to the pelvic bone. In addition, locally advanced vulvar cancer can refer to a patient with extensive lymphadenopathy in the groin(s). In other words, locally advanced vulvar cancer refers to patients for whom standard radical vulvar resection and bilateral inguinofemoral lymphadenectomy is not a surgical treatment option.[1–3] Treatment options for patients with locally advanced vulvar cancer are less standardized, resulting in a more individualized, multidisciplinary approach. Additionally, as the peak incidence of vulvar cancer is in patients aged 65–75 years, many patients are elderly and present with comorbidities. This makes vulvar cancer patients a vulnerable patient group.

The most commonly advised treatment options for patients with locally advanced vulvar cancer currently consist of an extensive surgical procedure, partial or total exenteration of the pelvis, or treatment with definitive chemoradiation.[1 2 4] Extensive surgery may require the construction of a permanent urostomy, colostomy, or both. Due to the extent of this surgery, it is associated with high morbidity rates, and a perioperative mortality rate of up to 2%.[5] Furthermore, patients often develop psychological problems due to major alterations in body image and loss of sexual function.[6] For patients that cannot undergo surgical treatment, primary chemoradiation has emerged as an alternative organ sparing treatment option in the past years. Currently, the National Comprehensive Cancer Network recommends chemoradiation with or without inguinofemoral lymphadenectomy as the treatment of choice for patients with locally advanced vulvar cancer.[7] However, evidence for the efficacy of this treatment strategy is still relatively limited. Most studies thus far are retrospective and present heterogeneous treatment regimens.[8 9]

The literature on effective treatment strategies for patients with locally advanced vulvar cancer is

scarce due to the rarity of the disease. However, it is important to search for other treatment options in this vulnerable patient group. Neoadjuvant chemotherapy followed by surgery is promising in other advanced gynecological cancer patients, such as ovarian cancer, selected endometrial cancer, and cervical cancer patients with bulky disease or in the scope of fertility preservation. In this setting, neoadjuvant chemotherapy is used to facilitate subsequent surgical treatment with decreased surgical morbidity and comparable oncological outcome. Preliminary case series showed that neoadjuvant chemotherapy can also be effective in patients with locally advanced vulvar cancer and can facilitate less mutilating and extensive surgery without compromising oncological outcome.[10–12]

To thoroughly investigate the efficacy and safety of neoadjuvant chemotherapy followed by surgery, we designed this randomized controlled trial in which we compare primary chemoradiation with neoadjuvant chemotherapy followed by surgery in patients with locally advanced vulvar cancer. The hypothesis of this trial is that neoadjuvant chemotherapy followed by surgery is oncologically safe, potentially more effective than primary chemoradiation in establishing long lasting locoregional control, and associated with less treatment-related morbidity.

METHODS

Trial Design

The VULCANize2 trial is a prospective, multicenter, phase II randomized controlled trial that compares the efficacy and safety of neoadjuvant chemotherapy followed by surgery (experimental treatment arm) with primary chemoradiation (standard treatment arm) for patients with locally advanced vulvar cancer that would otherwise require exenterative surgery. The study will start in the Netherlands at seven centers (Antoni van Leeuwenhoek, Amsterdam; Leiden University Medical Center; University Medical Center Groningen; Catharina Cancer Institute Eindhoven; University Medical Center Utrecht; Radboud University Medical Center, Nijmegen; and Amsterdam University Medical Center). In addition, we have the commitment of eight other European medical centers for participation in this study, including: University Hospital Leuven, Belgium; Mater Olbia Hospital, Sardinia, Italy; Faculty Hospital Kralovske Vinohrady, Prague, Czech Republic; Gemelli Hospital, Rome, Italy; Medical Faculty Lyon-Est, France; Metaxa Cancer Hospital, Piraeus, Greece; Karolinska University Hospital, Stockholm, Sweden; and Hospital Clinico Sarn Carlos, Madrid, Spain. The study is open to other interested centers.

After signing informed consent, patients included in the standard treatment arm will receive a combination of weekly cisplatin (total of 6 weeks) combined with 30 fractions of external beam radiotherapy on the primary tumor with a total dose of 64.5 Gy. Cisplatin will be given intravenously with a dose of 40 mg/m^2; in case of reduced kidney function (estimated glomerular filtration rate <50 mL/min), carboplatin 2 area under the curve (AUC) will be administered as an alternative. If a patient presents with bulky nodes, debulking will be performed before the start of chemoradiation. Patients included in the experimental arm will be treated with intravenous infusion of paclitaxel 175 mg/m^2, followed by carboplatin AUC 5. This will be administered every 3 weeks with preferably three, and a maximum of four, courses of chemotherapy. Neoadjuvant chemotherapy will subsequently be followed by radical surgery in responding patients. A 4–6 week interval after the last course of chemotherapy will be required before surgery, to allow sufficient physical recovery. If indicated, adjuvant radiotherapy of the vulva and/or groin(s) can be performed after surgery.

In all patients, treatment response will be evaluated with gynecological examinations, including pictures with a ruler in two directions during the treatment protocol, and a magnetic resonance imaging scan 12 weeks after finishing the treatment protocol. Follow-up from all included patients will be done every 3 months in the first 2 years and will include a physical examination and evaluation of adverse events (Figure 1).

Participants

All eligible patients must be aged ≥18 years and have a histologically confirmed primary or recurrent squamous cell carcinoma of the vulva, International Federation of Gynecology and Obstetrics (FIGO) stages Ib–IVa (lesions larger than 2 cm in size or stromal invasion larger than 1 mm (T1b or higher), any status of lymph node involvement (any N), no distant metastasis including pelvic lymph nodes (M0)). The local tumor size or localization of the tumor must require treatment through primary chemoradiation, or extensive surgery, meaning surgery damaging the pelvic organs or exenterative surgery. Patients with locally advanced vulvar cancer are often older and present with (multiple) comorbidities. To assure that patients can endure both treatment arms, a World Health Organization performance status of 0–2 is required. Furthermore, patients must have adequate hematological, hepatic, and renal function, as well as a low beta human chorionic gonadotropin level for women of childbearing potential. Patients will be excluded if they present with highly suspicious or positive metastases of the pelvic lymph nodes, had previous radiotherapy to the pelvis or groins, or have existing neuropathy which will hinder the administration of chemotherapy.

Primary Endpoints

The primary endpoint is locoregional control at 2 years. Secondary endpoints are disease related treatment failure, disease free survival, patterns of recurrence, overall survival, treatment related death, prevention of trimodal treatment (surgery, chemotherapy, and radiotherapy), functional organ preservation, and short and long term complications.

The main objective of this trial is to compare the efficacy and safety of primary chemoradiation with neoadjuvant chemotherapy followed by surgery in patients with locally advanced vulvar cancer. The secondary objective is to compare the quality of life in both patient groups. Patients will be asked to complete a questionnaires before treatment, and at 9 and 15 months after randomization. Furthermore, we will determine the effect of human papillomavirus status on treatment response.

Sample Size

A total of 98 eligible patients will be randomly allocated to one of the two groups. Locoregional control at 2 years for the chemoradiation arm is assumed to be 45%. We expect to improve this to 65% by treating patients with neoadjuvant chemotherapy followed by surgery. A sample size of 49 patients per treatment arm achieves

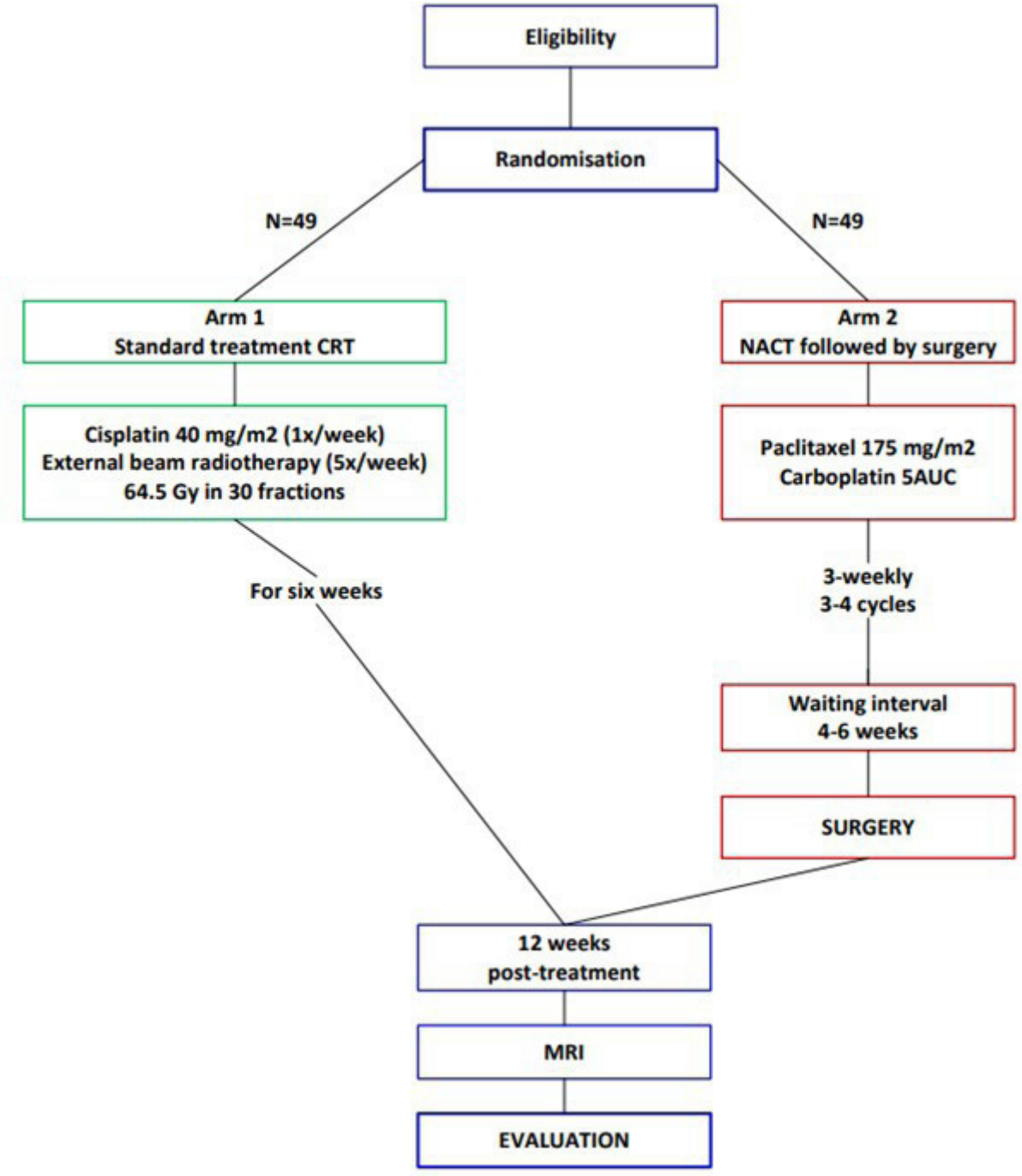

Figure 1 Trial design. AUC, area under the curve; CRT, chemoradiation therapy; NACT, neoadjuvant chemotherapy .

80% power to declare a difference between treatment arms as significant at a two-sided 10% significance level.

No interim analyses for efficacy are planned. A bayesian stopping rule will be implemented. The maximum probability of progression during neoadjuvant chemotherapy is defined as 10%. If there is more than 80% probability that the progression rate exceeds 10%, the trial will be considered unsafe and potentially stopped. Safety evaluation will start after 10 patients are accrued. After each subset of five patients is enrolled, the posterior probability of progression rate exceeding 10% will be calculated. The data and safety monitoring board will be asked to review the data. The stopping boundaries are calculated using Jack Lee's bayesian efficacy/safety monitoring via posterior probability.

Randomization and Blinding

Randomisation will be stratified for stage of disease (T1b or larger tumor with (irresectable) groin metastases vs T1b or larger tumor with involvement of the urethra or anal sphincter) to prevent heterogeneous patient groups. There will be no blinding to treatment.

Statistical Methods

The difference between the two treatment arms will be tested using a log rank test. Disease related failure and incidence will be

illustrated using a Kaplan–Meier curve. Subsequently, the efficacy of treatment by including competing events in the data analysis will be studied. For this, a survival analysis model using the subdistribution hazard method of Fine and Gray will be used.[13] The competing events considered here are, for example, death due to other causes, as well as the occurrence of another disease (due to comorbidity), preventing the treatment to continue. As this model also allows for the correction of effects of other clinical variables on survival probability, it will be used to study the effect of positive inguinal lymph nodes and tumor size at the start of treatment.

DISCUSSION

Patients with locally advanced vulvar cancer often represent a frail patient group with multiple comorbidities. Current treatment options include extensive surgery or chemoradiation; both of these modalities are associated with high morbidity rates and complications. The VULCANize2 trial will initiate a multicenter collaboration to focus on new treatment options for patients with locally advanced vulvar cancer. Research in this field has been hampered by the fact that vulvar cancer is a rare malignancy. The lack of multicenter and international collaborations have contributed to the dearth of solid evidence. As vulvar cancer mostly occurs in an elderly population, studies on the effectiveness of novel treatments are also scarce due to the frailty of this population. This trial represents an important stepping stone for patients with vulvar cancer.

The hypothesis of this trial is that neoadjuvant chemotherapy followed by surgery is more effective than primary chemoradiation in establishing long lasting locoregional control, giving the opportunity for combining organ sparing treatment with an improved prognosis. Earlier small case series have shown promising results using neoadjuvant chemotherapy in locally advanced vulvar cancer . In 2018, Amant et al treated two patients with locally advanced vulvar cancer with carboplatin–paclitaxel chemotherapy and observed an impressive response. Combination with vulvar surgery resulted in long term disease control.[12] Adorni et al conducted a retrospective study of 15 locally advanced vulvar cancer patients treated with neoadjuvant chemotherapy followed by surgery in 2021. The overall response of the vulvar tumor for neoadjuvant chemotherapy was 66% (20% complete response and 46% partial response). The overall response for inguinal lymph nodes was 69% (23% complete response and 46% partial response). Five year survival was 60%.[10] Lastly, another excellent response of two locally advanced vulvar cancer patients treated with neoadjuvant chemotherapy (paclitaxel, carboplatin, and bevacizumab) was reported by Klavans et al. Both patients had a significant reduction in the size of their primary tumor (FIGO stage IV) and sites of metastases.[11]

We expect that VULCANize2 will spearhead research in this field, galvanize future studies, and solidify multicenter collaborations. In particular, we will create a national (and European) vulvar cancer working group, with the aim of facilitating studies by consolidating clinical data and creating biobanks. This study is a unique opportunity to evaluate the efficacy and safety of primary chemoradiation compared with neoadjuvant chemotherapy followed by surgery to prevent trimodal treatment in a relatively large group of patients with a rare tumor. If our hypothesis is proven to be true, it can have a large impact on treatment modalities for locally advanced vulvar cancer. It will enable more treatment options in this often frail patient group, improve locoregional control, and also lower treatment complications. Therefore, VULCANize2 has the potential to improve the prognosis and quality of life of locally advanced vulvar cancer patients.

Author affiliations
[1]Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University Hospitals Leuven, Katholieke Universiteit Leuven, Leuven, Belgium
[2]Gynecology, Netherlands Cancer Institute, Amsterdam, Netherlands
[3]Gynecology, Leiden University Medical Centre, Leiden, Netherlands
[4]Medical Oncology, University Medical Center Groningen, Groningen, Netherlands
[5]Radiation Oncology, Netherlands Cancer Institute, Amsterdam, Netherlands

Contributors All authors have provided substantial contribution and are in agreement with all aspects of the final manuscript. FA: guarantor, conceptualization, methodology, review, and supervision. AFvV: writing original draft. AR: conceptualization, methodology, and review. HZ: conceptualization, methodology, and review. EES: conceptualization, methodology, review, and supervision. LN: conceptualization, methodology, review, and supervision.

Funding The study is funded by the Koningin Wilhelmina Fonds (KWF).

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval The trial was approved by the Dutch medical ethical committee (EU-CT 2022-502685-25-00) and supported by the Dutch Gynecologic Oncology Group. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; internally peer reviewed.

Data availability statement There are no data in this work.

ORCID iDs
Frédéric Amant http://orcid.org/0000-0002-5452-4905
Anne Fleur van Velzen http://orcid.org/0009-0008-7421-1237
Linda Nooij http://orcid.org/0000-0001-5741-4595

REFERENCES

1 Gadducci A, Aletti GD. Locally advanced squamous cell carcinoma of the vulva: A challenging question for gynecologic oncologists. *Gynecol Oncol* 2020;158:208–17.
2 Graham K, Burton K. Unresectable vulval cancers: is neoadjuvant chemotherapy the way forward *Curr Oncol Rep* 2013;15:573–80.
3 Niu Y, Yin R, Wang D, *et al*. Clinical analysis of neoadjuvant chemotherapy in patients with advanced vulvar cancer: A STROBE-compliant article. *Medicine (Baltimore)* 2018;97:e11786.
4 Mahner S, Prieske K, Grimm D, *et al*. Systemic treatment of vulvar cancer. *Expert Rev Anticancer Ther* 2015;15:629–37.
5 Matsuo K, Mandelbaum RS, Adams CL, *et al*. Performance and outcome of pelvic exenteration for gynecologic malignancies: A population-based study. *Gynecol Oncol* 2019;153:368–75.
6 Gadducci A, Cionini L, Romanini A, *et al*. Old and new perspectives in the management of high-risk, locally advanced or recurrent, and metastatic vulvar cancer. *Crit Rev Oncol Hematol* 2006;60:227–41.
7 Koh W-J, Greer BE, Abu-Rustum NR, *et al*. Vulvar cancer, version 1.2017, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw* 2017;15:92–120.
8 Shylasree TS, Bryant A, Howells RE. Chemoradiation for advanced primary vulval cancer. *Cochrane Database Syst Rev* 2011.
9 van Doorn HC, Ansink A, Verhaar-Langereis M, *et al*. Neoadjuvant chemoradiation for advanced primary vulvar cancer. *Cochrane Database Syst Rev* 2006.
10 Adorni M, Bazzurini L, Lissoni AA, *et al*. Neoadjuvant chemotherapy followed by radical surgery in locally advanced vulvar carcinoma: a single-institution experience. *Tumori* 2022;108:495–501.
11 Klavans MR, Erickson SH, Modesitt SC. Neoadjuvant chemotherapy with paclitaxel/carboplatin/bevacizumab in advanced vulvar cancer: time to rethink standard of care. *Gynecol Oncol Rep* 2020;34.
12 Amant F, Nooij L, Annibali D, *et al*. Brief report on 3-weekly paclitaxel carboplatin efficacy in locally advanced or metastatic squamous vulvar cancer. *Gynecol Obstet Invest* 2018;83:620–6.
13 Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999;94:496–509.