Groningen International Study on Sentinel nodes in Vulvar cancer - III, a prospective phase II treatment trial

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This study has been transitioned to CTIS with ID 2023-508722-99-00 check the CTIS register for the current data. Primary objective:- Investigate the safety of replacing inguinofemoral lymphadenectomy by chemoradiation in early stage vulvar cancer...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Reproductive neoplasms female malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON53136

Source
ToetsingOnline

Brief title
GROINSS-V III

Condition

- Reproductive neoplasms female malignant and unspecified

Synonym
vulvar cancer

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: er wordt financiering aangevraagd bij het KWF;call 2019-1. Repons wordt juni 2019 verwacht.

Intervention

Keyword: chemoradiation, metastasis, sentinel node, vulvar cancer

Outcome measures

Primary outcome

Primary endpoint:

- Groin recurrence rate in the first two years after primary treatment

Secondary outcome

Secondary endpoint:

- Treatment related morbidity (CTC AE v 4.0)

- Disease-specific and overall survival

- Patient-reported quality of life

Study description

Background summary

GROINSS-V I showed that omission of inguinofemoral lymphadenectomy is safe in patients with a negative SN. In an in-depth analysis of GROINSS-V-I data, for which we reviewed 723 SNs, it was shown that in patients with SN metastases <= 2mm additional metastases were observed in 3/43 patients (7%) and in patients with SN metastases > 2mm in 12/36 (33%). In GROINSS-V II, patients with a positive SN were treated with radiotherapy instead of inguinofemoral lymphadenectomy in order to reduce morbidity. While the final results are pending, in GROINSS-V II, interim analysis of patients with a positive SN that were treated with radiotherapy (50 Gy) so far showed 3% groin recurrence rate in patients with SN metastases <= 2mm and 18% in patients with SN metastases > 2mm. These preliminary data show that there is effect of radiotherapy (50 Gy, given at the right depth and localization), but that the dose is not enough to eradicate macrometastatic disease in the absence of a full lymph node dissection.
The efficacy of radiotherapy can be increased by either increasing the dose and / or adding concurrent chemotherapy. It is well known from other (HPV-related) squamous cell carcinomas that adding chemotherapy as a radiosensitizer during radiotherapy improves both local control and survival. In cervical cancer,

several studies and meta-analyses demonstrated the beneficial effect of adding chemotherapy, both in the primary and adjuvant setting. A Cochrane meta-analysis and several small studies of neoadjuvant or primary chemoradiation for vulvar cancer showed high response rates and up to 64% clinical complete remission rates [15-18]. In general the addition of chemotherapy to radiotherapy will increase the effectiveness of treatment with 20-25% (relative increase in complete remission/local control), which translates in general in 10% absolute benefit of the addition of chemotherapy. In studies on chemoradiation in cervical cancer there is remarkable symmetry in the reduction of relative risk of relapse or death by 30-50%. In a large population-based analysis, addition of chemotherapy resulted in a significant 38% reduction in mortality risk for node-positive vulvar cancer patients who received adjuvant radiotherapy.

Study objective

This study has been transitioned to CTIS with ID 2023-508722-99-00 check the CTIS register for the current data.

Primary objective:
- Investigate the safety of replacing inguinofemoral lymphadenectomy by chemoradiation in early stage vulvar cancer patients with a macrometastasis (>2mm) and/or extracapsular extension in the sentinel lymph node

Secondary objectives:
- Evaluate the short and long-term morbidity associated with the sentinel node procedure and chemoradiation

Study design

A prospective phase II treatment trial of chemoradiation will be performed in patients with early stage SCC of the vulva and a macrometastasis in their SN. Eligible for SN detection are patients with a T1 SCC of the vulva, < 4cm in diameter, depth of invasion > 1mm, and no suspicious lymph node at imaging of the groins (ultrasound, CT or MRI). Patients with SN metastases > 2mm and / or with extracapsular spread will be eligible for this study. Patients with > 1 micrometastasis can also be included.
Dose schedule:
Cisplatin 40 mg/m2 intravenously on days 1, 8, 15, 22 and 29 of RT
- In case of renal impairment (creatinine clearance between 40-60 mmol/ml) cisplatin 20mg/m2 or carboplatin AUC2 can be given.
- In case of significant other comorbidities an alternative schedule of weekly carboplatin AUC2 can be used on days 1, 8, 15, 22 and 29 .
Radiotherapy: 56 Gy to the involved inguinal site. A dose of 48-50 Gy in 1.8 Gy daily fractions will be given to the inguinofemoral and external iliac nodal regions, with a boost dose to the involved site for a total dose of 56 Gy over

5-6 weeks, preferably with simultaneous integrated boost technique.

Intervention

When definitive histopathological examination shows a SN metastasis > 2mm and/or extracapsular extension, chemoradiation will be given: in principle only the side with the metastatic involved side of SN is treated in case of bilateral SN with only one side with metastases. Depending on the pathologic evaluation of the primary vulvar cancer (radicality, size, presence of extensive LVSI) the vulva may be included in the target volume on an individual basis.

Study burden and risks

Radiotherapy and chemotherapy are associated with other side effects than standard treatment (lymphadenectomy). During treatment there might be complaints of nausea, vomiting, diarrhea or obsitpation.

The treatment is a combination of radiotherapy and chemotherapy, possibly results in less longterm morbidity (less lymphedema, less infections) compared to the standard treatment (full lymphadenectomy).
After treatment there is always a risk of disease recurrence in the groin. After standard treatment this risk is approximately 10%. The risk might be higher after chemoradiation.

Contacts

Public
Universitair Medisch Centrum Groningen

Hanzeplein 1
Groningen 9713GZ
NL
Scientific
Universitair Medisch Centrum Groningen

Hanzeplein 1
Groningen 9713GZ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Histological confirmed primary SCC of the vulva
- T1 tumor, not encroaching urethra/vagina/anus
- Depth of invasion > 1mm
- Tumor diameter < 4cm
- Unifocal tumors
- No enlarged (>1.5cm) or suspicious inguinofemoral lymph nodes at imaging (CT/MRI/ultrasound)
- Possibility to obtain informed consent
- Metastatic sentinel lymph node; size of metastasis > 2mm
- Metastatic sentinel lymph node: more than 1 SN with metastasis <= 2mm
- Adequate bone marrow, renal and liver function:
• Absolute neutrophil count >= 1.5 x 109 /L
• Platelet count >= 100 x 109 /L
• Creatinine clearance >= 40 ml/min measured by the Cockroft Gault formula
• Total bilirubin < 1.25 x ULN
• Aspartate transaminase (AST) and alanine transaminase (ALT) <= 2.5 x ULN
- Performance status of 0, 1 or 2 on the Eastern Cooperative Oncology Group (ECOG) Scale
- Age 18 years or older
- Life expectancy of >= 12 weeks

Exclusion criteria

- Inoperable tumors and tumors > 4cm
- Multifocal tumors
- Tumors with other pathology than squamous cell carcinoma
- Patients with enlarged / suspicious lymph nodes which are proven metastatic after fine needle aspiration cytology
- No other carcinomas, other than basal cell carcinomas, within last 5 years

- History of pelvic radiotherapy
- History of any infection requiring hospitalization or antibiotics within 2 weeks before enrollment
- Pregnant female or nursing mother
- Unstable angina, myocardial infarction, cerebrovascular accident, > Class II congestive heart failure according to the New York Heart Association Classification for Congestive Heart Failure within 6 months before enrollment

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	12-03-2021
Enrollment:	80
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	carboplatin
Generic name:	carboplatin
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	cisplatin
Generic name:	cisplatin
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	27-02-2019
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	28-07-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	02-11-2020
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	16-09-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	28-03-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	11-01-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	28-03-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	05-07-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	29-01-2024

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	20-02-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2023-508722-99-00
EudraCT	EUCTR2016-003973-16-NL
CCMO	NL60164.042.18