Sentinel lymph node procedure in patients with recurrent vulvar squamous cell carcinoma.

A multicentre observational study.

V2SLN
SENTINEL NODE PROCEDURE IN RECURRENT VULVAR CANCER

Version 2.0

March 2nd, 2020

PROTOCOL TITLE *Sentinel lymph node procedure in patients with recurrent vulvar squamous cell carcinoma. A multicentre observational study.*

Protocol ID	**NL70149.078.19** **OZBS82.19089**
Short title	Sentinel Node Procedure in Recurrent Vulvar carcinoma.
EudraCT number	Not applicable
Version	2.0
Date	March 2nd, 2020
Coordinating investigator/project leader	H. (Lena) C. van Doorn MD, PhD Department of Gynaecologic Oncology Erasmus MC Cancer Institute, Rotterdam
Principal investigator	H. (Lena) C. van Doorn, MD, PhD Department of Gynaecologic Oncology Erasmus MC Cancer Institute, Rotterdam
Sponsor	Erasmus MC Cancer Institute, Rotterdam
Subsidising party	Not applicable
Independent expert	H. P. M. (Dineke) Smedts, MD, PhD, Gynaecologic-oncologist, Department Obstetrics and Gynaecology. Amphia Ziekenhuis, Breda
Writing committee	Heleen J. van Beekhuizen, MD, PhD, Department of Gynaecologic Oncology, Erasmus MC Cancer Institute, Rotterdam Guus Fons, MD, PhD, Department of Obstetrics and Gynaecology, AMC, Amsterdam Katja N. Gaarenstroom, MD, PhD, Department of Obstetrics and Gynaecology, LUMC, Leiden Joanne de Hullu, MD, PhD, Department of Obstetrics and Gynaecology, Radboud University, Nijmegen

	Maaike H.M. Oonk, MD, PhD, Department of Obstetrics and Gynaecology, UMCG, Groningen Joost M. van Rosmalen. Department of Biostatistics, Erasmus MC, Rotterdam
Laboratory sites	Not applicable
Pharmacy	Not applicable

PROTOCOL SIGNATURE SHEET

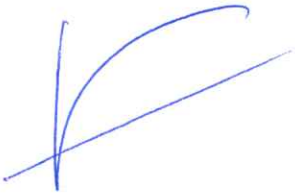
Name	Signature	Date
Head of Department of Gynaecologic Oncology, Erasmus MC, Rotterdam: Dr. H.J. van Beekhuizen		2/3/2020
Coordinating investigator/project leader/Principal Investigator Erasmus MC, Rotterdam: Dr. H.C. van Doorn, MD, PhD Gynaecologist		2-3-2020
Name site: Name Principal Investigator:		

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)**
AE	**Adverse Event**
AR	**Adverse Reaction**
CA	**Competent Authority**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CV	**Curriculum Vitae**
DSMB	**Data Safety Monitoring Board**
EU	**European Union**
EudraCT	**European drug regulatory affairs Clinical Trials**
GCP	**Good Clinical Practice**
GDPR	**General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG)**
IB	**Investigator's Brochure**
IC	**Informed Consent**
IFL	**Inguinal-femoral lymph node dissection**
IMP	**Investigational Medicinal Product**
IMPD	**Investigational Medicinal Product Dossier**
METC	**Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)**
(S)AE	**(Serious) Adverse Event**
SLN	**sentinel lymph node**
SPC	**Summary of Product Characteristics (in Dutch: officiële productinfomatie IB1-tekst)**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**

UAVG	**Dutch Act on Implementation of the General Data Protection Regulation; in Dutch: Uitvoeringswet AVG**
WMO	**Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale: Standard groin treatment in recurrent vulvar cancer consists of a uni or bilateral inguinal lymph node dissection (IFL), whereas in the primary setting a sentinel lymph node (SLN) procedure is performed in case of unifocal tumours < 4cm without suspicious groin lymph nodes at imaging. The advantages of SLN procedure over an IFL are obvious: the short and long term sequels such as wound healing problems, lymph cyst formation, recurrent erysipelas and lymph oedema are much less common after SLN procedure. In a national retrospective analysis we showed that SLN is feasible in selected recurrent vulvar cancer patients. This national prospective observational study aims to investigate the safety of such procedure.
Since little is known on the outcome of 1st recurrent vulvar cancer we also gather more information on women with a first recurrence, not eligible for the SLN procedure.

Objective: The primary objective is to investigate the safety of replacing complete IFL by the SLN procedure in patients with local recurrent vulvar squamous cell carcinoma without suspicious groin lymph nodes.

Study design: This is predominantly a prospective multicentre observational study on sentinel lymph node (SLN) procedure in women with local recurrent vulvar cancer. Besides it is an observational study on the treatment and outcome of women with a local recurrent vulvar cancer, not eligible for the SLN procedure.

Study population: Women with their first local recurrence of vulvar cancer, 18 years and older, fit for surgical treatment, who had previous groin treatment as part of the primary treatment: none, uni- or bilateral SLN procedure, or IFL and/or radiotherapy. Excluded are women with previous ipsilateral IFL and radiotherapy, or bilateral IFL and radiotherapy. Women that do not fulfil these criteria will be included in the observational arm.

Intervention: Surgical treatment consists of standard local treatment (wide local resection, vulvectomy) of the vulvar tumour combined with a uni- or bilateral SLN procedure.

Main study parameters/endpoints: Primary end point is the number of groin recurrences after SLN procedure. Secondary endpoints: success rate of the SLN procedure, surgical drawbacks, wound healing problems, long term sequela, and quality of life in women treated for a 1st recurrent vulvar cancer.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: In this study, similar to the current routine, preoperative imaging of chest, abdomen and groins is performed. The patient is informed about the standard procedure and about the option of a SLN procedure. She and her treating gynaecologist decide on the preferred treatment. Prior to surgery the planned surgical procedure is recorded, including patients' consent for IFL in case the SLN procedure fails. The surgical procedure (SLN procedure) will be less extensive compared to routine IFL, with less unfavourable short and long term effects, such as infections and lymph oedema. In case of groin metastases detected in the SLN procedure further treatment is warranted, either by surgery (uni or bilateral IFL) and/or by radiotherapy. At follow up participants will undergo (non-invasive) ultrasonography studies of the groin at 6 and 12 months. Participants will be asked to fill in additional questionnaires at baseline, 6 and 12 months. In case of a groin recurrence (due to failed SLN procedure) further treatment is warranted, probably resulting in a poorer prognosis with a high mortality rate (probably 80-90%). Currently, robust data on the occurrence of groin recurrence after either SLN biopsy or IFL for recurrent vulvar cancer is lacking. Given the lower morbidity and less short and long term side effects of the SLN procedure compared to IFL an additional 5% failure rate is considered acceptable.

1. INTRODUCTION AND RATIONALE

The treatment for vulvar cancer has changed over the last decades. Currently the standard treatment for unifocal squamous cell carcinoma (SCC) of the vulva < 4 cm diameter without suspicious inguinofemoral lymph nodes at imaging consists of wide local excision and sentinel lymph node (SLN) procedure of the inguinofemoral lymph nodes (1-4). The advantages of SLN procedure over an inguinofemoral lymphadenectomy (IFL) are obvious: the short and long term sequels such as wound healing problems, lymph cyst formation, recurrent erysipelas and lymph oedema are much less common after SLN procedure (4). Lymphedema and recurrent erysipelas were seen in respectively 1.9% and 0.4% after SLN procedure and in respectively 25.2% and 16.2% after inguinofemoral lymphadenectomy (4). Groin recurrences after negative SLN procedures in primary vulvar SCC patients were reported in 2–3% of the patients (1, 5, 6). Unfortunately, a groin recurrence after IFL have a very high mortality rate, the prognoses after a negative SLN procedure is unclear; therefore very strict criteria with respect to tumour characteristics, preoperative and pathological assessment and surgical technique should be met to guarantee the safety of the SLN procedure and to minimize the number of false negative results and the risk of groin recurrence. Local recurrences of SCC of the vulva are reported in 20–46%(7). Many of these recurrences might be second primary tumours in a background of lichen sclerosis and differentiated vulvar intraepithelial neoplasia or high grade squamous cell intraepithelial lesion (HSIL) of the vulva rather than a real recurrence(8, 9). In patients with recurrent vulvar SCC, IFL is considered standard treatment for patients who previously did not undergo an IFL(10). So, in case of a local recurrence, only after bilateral IFL groin surgery is omitted. Since many of these patients are elderly and frail an alternative treatment other than IFL may be justified to avoid or reduce long term morbidity in this particular group of patients. In a retrospective analysis of it was shown that in a considerable number of patients groin surgery is not performed, in contrast with the guideline. In a retrospective study including 200 women with a macro invasive local recurrence the risk for groin metastases was 18%, and related to depth of invasion and tumour diameter. (Personal communication Anne-Floor Pouwer[1]). The lower percentage of groin lymph node metastases in case of a local recurrence compared to primary SCC is probably explained by earlier diagnosis due to standard follow-up.

[1] Incidence and risk factors for inguinofemoral lymph node metastasis in patients with a local recurrence of vulvar squamous cell carcinoma. Anne-Floor W. Pouwer, Martijn H.A. Mensink, Nienke C. te Grootenhuis, Leon F.A.G. Massuger, Maaike H.M. Oonk, Joanne A. de Hullu. Abstract 2018

Recently we performed a national multicentre retrospective study and showed that in recurrent vulvar SCC repeat SLN procedure seems feasible: in 77% of 27 patients and in 84% of the 44 groins the SLN procedure could be performed as planned (11). The SLN procedure appears technically more challenging in recurrent vulvar SCC compared to initial surgery. In two groins, SLNs were found at unpredicted localizations, beyond the borders of normal IFL. Four lateral tumours showed bilateral SLNs. Data on safety are lacking but so far none of the patients with a negative SLN procedure in this study suffered from groin or distant recurrences after these SLN procedures after a median follow up of 27 months (range 2–96 months). We concluded from this retrospective study that the SLN procedure might be helpful in the visualization of the lymph drainage and guides the gynaecologic oncologist in the removal of the lymph nodes at risk. This conclusions was described earlier in recurrent breast cancer(12).

The current protocol is an observational study on the safety and efficacy of the SLN procedure in the first local recurrence of vulvar SCC. An accuracy study, in which a SLN procedure is followed by an IFL, seems not feasible due to the low incidence. Since our preliminary data show that in recurrent vulvar SCC the SLN procedure could be placed beyond the borders of the normal IFL, a SLN might reveal unsuspected metastases. Women might opt for a SLN procedure even when they refuse an IFL, thereby offering SLN will increase protocol adherence. As a second best we have therefore chosen for an observational study design with stopping rules.

2. OBJECTIVES

Primary Objective:

To investigate the safety of replacing complete IFL by SLN procedure in women with a first recurrent vulvar SCC in tumours < 4 cm.

Secondary Objectives:

1) To investigate the feasibility of the SLN procedure in patients with a first recurrence of vulvar SCC. (Success rate of the SLN procedure, surgical drawbacks)
2) To evaluate the short and long-term morbidity associated with the sentinel lymph node procedure in patients with a first recurrence of vulvar SCC.(complications, wound healing problems, long term sequela, quality of life)
3) To evaluate the short and long-term morbidity associated with treatment of a first recurrence of vulvar SCC.(complications, wound healing problems, long term sequela, quality of life)

3. STUDY DESIGN

Preferably a randomized clinical trial or a non-inferiority study should be performed to answer the questions of this study. Given the low incidence of vulvar cancer and the even lower incidence of recurrent vulvar cancer it is not feasible to perform a study other than a multicentre cohort study.

In the participating centres all patients older than 18 years, fit for surgical treatment, with a first vulvar cancer recurrence will be registered.
Standard imaging (i.e., chest, abdominal and groin CT scanning) is performed.
In the absence of distant or proven groin metastases, and when all other eligibility criteria (see Figure 1) are met, the study is proposed and discussed with the patient.
Patients will be informed by oral and written information about the standard treatment (i.e. IFL) and the SLN procedure as part of the study. Patients will be informed that it is possible that the SLN is not traced after injection or at surgery. They will be informed that, should this be the case, standard treatment should be uni- or bilateral IFL. However, from our retrospective study it has become obvious that not all patients will consent for groin treatment and particularly IFL. So three patient groups are identified in *the SLN cohort*: (Figure 1)

A) Control group: patients who understand the study and choose the standard IFL treatment of the groin(s): These patients will be asked to participate in the conventional treatment arm, with similar questionnaires and follow up.
B) Patients understanding the study and are willing to undergo a SLN procedure rather than IFL.
   B1) Patients who agree on IFL(s) in case the SLN is not visible on the lymph scintigram, or not detected at surgery
   B2) Patients who not agree on IFL(s) in case the SLN is not visible on the lymph scintigram, or not detected at surgery
C) Patients who agree on vulvar surgery, but refuse any groin surgery. These patients will be asked consent to collect information regarding treatment and outcome, and to fill in the questionnaires.

After surgery *regular follow up* is planned, with visits at 3, 6, 9, 12, 15, 18, 21 and 24 months. For study purposes ultrasonography of the groins is performed at 6 and 12 months. At baseline, at 6 and 12 months QoL questionnaire and a lymph oedema query are requested (see 4.1.3. for questionnaires).

All women with a first vulvar recurrence not eligible for the SLN procedure, unless not capable to read Dutch or English, will be asked to participate in the observational arm of *the non- SLN cohort*. For this purpose a different patient information folder and different consent forms are applicable. They will receive standard (personalised) treatment and follow up. They will be requested to fill in questionnaires at baseline, 6 and 12 months and if they agree on storage and use of any tumour tissues.

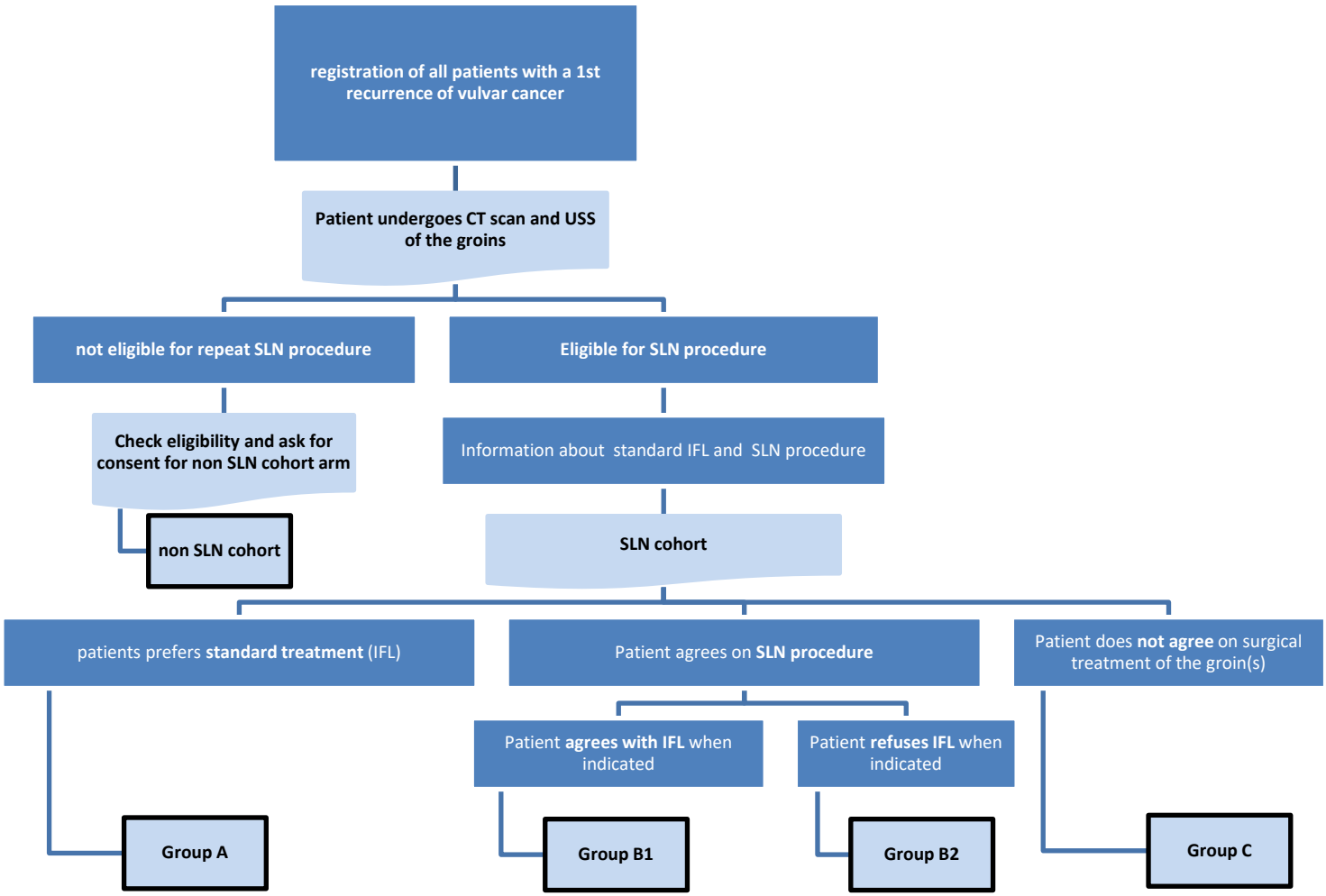


Figure 1 Flow diagram of patients with a 1st recurrence of vulvar SCC

4. STUDY POPULATION

4.1 Population

In the Netherlands vulvar cancer treatment is centralised in university hospitals and cancer clinics. The annual incidence is rising due to the aging population and due to the increase in HPV related vulvar cancer.[www.iknl.nl] A local recurrence occurs in 20-40% of the women.(13) Although IFL is the standard treatment in local recurrent vulvar cancer, more and more clinics perform a SLN procedure, without data on feasibility and safety. Therefore the willingness of the gynaecologic oncologists to participate in this study is high. However, previous national studies (GROINSS-V and GROINS-VII) have shown that a study like this will take a lot of time. We expect that the willingness of patients to participate in this study will be 80% or above, since they can opt for standard treatment or study treatment rather than being randomized.

4.2 Inclusion criteria

In order to be eligible for the study (non SLN cohort and SLN cohort, group A-C):

- Possible to understand and read Dutch.
- Possible to understand the study and give informed consent.
- No age limit specified.
- Patients should mentally, physically and geographically be able to undergo follow-up.

In order to be eligible to undergo the SLN procedure, a subject must meet all of the following criteria:

- First local recurrent SCC of the vulva.
- Previous treatment with wide local excision or (partial) vulvectomy tumours < 4 cm., not encroaching in urethra, vagina or anus with clinically negative inguinofemoral lymph nodes.
- Localisation and size of the tumour are such that perilesional injection of the tracers at three or four sites is possible.
- Preoperative imaging does not show enlarged (> 10 mm sort axis) or suspicious nodes.
- Fit for surgery

4.3 Exclusion criteria

A potential subject who meets any of the following criteria should not undergo the SLN procedure in the study arm (A-B), the patient can be asked for the non SLN cohort.

- Inoperable tumours and tumours with diameter > 4 cm.
- Patients with inguinofemoral lymph nodes at palpation clinically suspect for metastases, at radiology enlarged (> 10 mm short axis) / suspicious groin nodes and with cytological proven inguinofemoral lymph node metastases.
- A history of bilateral IFL **and** radiotherapy to the groins.
- A lateral tumour and history of ipsilateral IFL **and** ipsilateral radiotherapy.
- Tumour encroaching urethra, vagina, or anus.
- Previous surgery of the vulva was not radical (margin < 1 mm) and additional treatment (2nd surgery or radiotherapy) was not performed.
- Multifocal recurrent disease of the vulva.
- Synchronous, non- curable 2nd malignancy.

4.4 Sample size calculation

Approximately 18% of women will have groin metastases at the moment of their first vulvar cancer recurrence. Of these, approximately 20% will be detected prior to surgery (based on imaging and FNA) and these women will not be offered a SLN procedure, but advised to undergo an IFL(s). They will be asked for the observational arm of the non SLN cohort. (See figure 2)

The remaining patients will be informed about the study, they can decide on standard IFL (group A) or refuse any surgery of the groin(s) (group C) In 75% of cases that undergo SLN (group B) it will be possible to retrieve the SLN. In approximately 14,5% of women undergoing a SLN procedure a tumour positive node will be present. It is not expected that the change of a successful SLN procedure relates to the presence or absence of a positive groin node. We expect to find a positive SLN in 11% of cases undergoing a SLN procedure, a negative SLN in 64%, and an unsuccessful procedure in 25%. This corresponds to respectively 10.5%, 61.8% and 24.1% of all included patients.

Percentage failure of SLN or IFL is known for neither procedure in the recurrent setting. In the primary setting groin recurrence after negative IFL and after negative SLN are both about 3%.

Sample size for V2SLN is calculated based on a conservatively estimated groin recurrence rate of 3%, with a maximum additional groin failure rate of SLN in local recurrent vulvar SCC of 5%. The sample size, considering an alpha of 0.10 and a beta of 0.20, is then calculated to be 150 patients with a first vulvar cancer recurrence undergoing a SLN procedure (group B) and a negative SLN (Figure 2) So, we expect that approximately 243 women with a 1st recurrence of vulvar cancer should be included in the study. Stopping rules with dynamic boundaries were constructed to guarantee the safety of the study by continuously monitoring the number of groin recurrences. See Appendix 1 for a detailed description of these stopping rules.

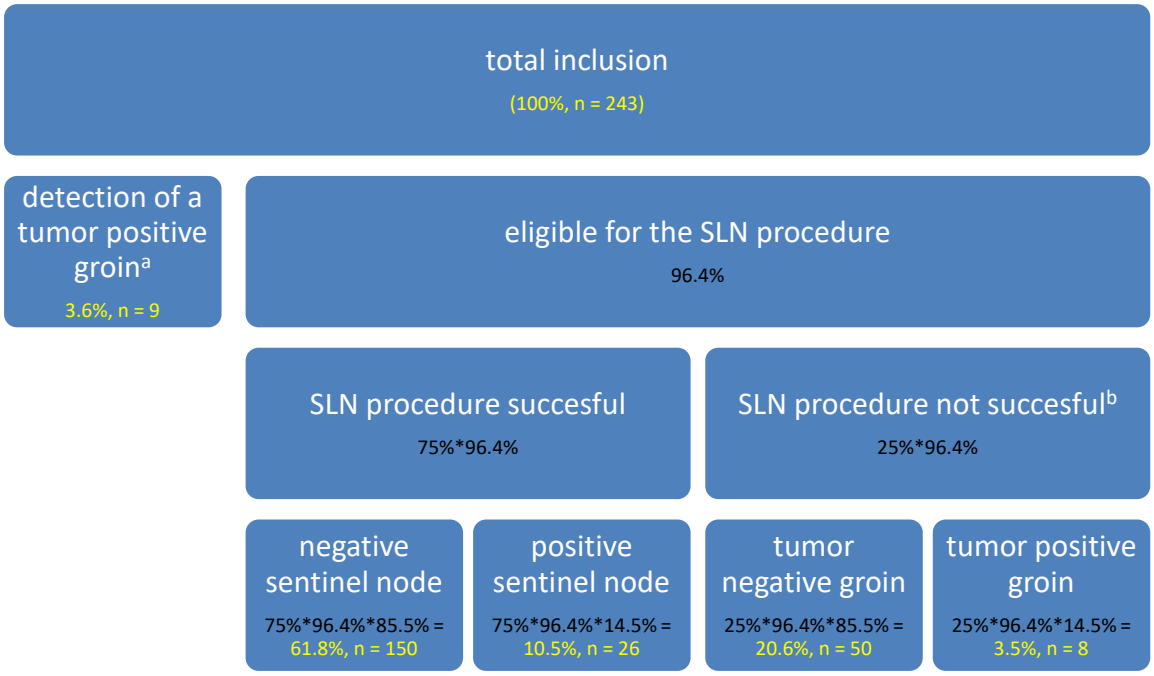


Figure 2 Flow diagram of calculation of sample size

5. TREATMENT OF SUBJECTS

5.1 Investigational product/treatment

Participants will be informed that IFL is the standard treatment. However they can opt for an alternative treatment: the SLN procedure. They will be informed that it is not known yet if this SLN procedure is as safe as IFL, however that short and long time sequels like lymph oedema and recurrent erysipelas are less frequent in the SLN group based on data of primary vulvar SCC. The surgical SLN procedure will be performed as per protocol. The SLNs are removed and sent separately for pathologic examination (including ultra-staging with immunohistochemistry).

5.1.1 Preoperative assessment

In accordance with current routine pre-operative imaging of the chest, abdomen and inguinal area is done by CT scan. In case of enlarged (> 10mm short axis) or suspicious nodes ultrasound of the groins with FNA should be performed to rule out metastatic involvement. When FNA is negative, patients can proceed to SLN procedure, the gynaecologic oncologist should in these cases be ensured that at least all (suspicious) enlarged nodes are removed.

5.1.2 Preoperative definition of planned surgery

Prior to surgery the gynaecologic oncologist has to state what groin surgery should be done; ipsi or bilateral groin treatment and what treatment should be done in case the SLN is not visible, or not found during surgery. This decision relates to the previous groin treatment and whether or not the tumour crosses the midline. (See figures planned surgery). All SLN shown by imaging should be removed, also contralateral nodes in lateral tumours, and nodes in groins previously treated with IFL or radiotherapy, unless stated otherwise prior to surgery. In the current (standard) treatment protocol (www.oncoline.nl) groin surgery is not performed in local recurrent vulvar cancer after a previous IFL. Women should have an IFL in case of technical problems (SLN does not appear on the scintigraphy, or cannot be retrieved at surgery). Women that do not consent for a full IFL in case of technical problems (SLN does not appear on the scintigraphy, or cannot be retrieved at surgery), are more likely to experience groin recurrences (post-priory 17%).
When women do not consent for IFL this should be noted prior to surgery.

Figures flow charts planned surgery see addendum 2.

5.1.3 Sentinel node detection protocol

Three to 24 hours before the surgical procedure, 0.5 ml 30 - 100 MBq (depending on the local protocol, interval between injection and surgery, sensitivity of the probe etc.) 99mTc-labeled Nano colloid with a particle size < 80 nm is injected circumferentially intradermal on 4 locations around the primary tumour. In accordance with local protocols IGN labelled Nano colloid is used. Half an hour before the injections lidocaine-prilocaine 5% cream will be applied on the vulva for pain relief. Anterior images are obtained using a single head gamma camera with a low energy high resolution collimator. Within 5 minutes after injection dynamic imaging is started within 30 sec frames during 30 minutes. A static image is obtained after 2.5 hours. In order to facilitate interpretation transmission scanning will be done simultaneously using the 120 KeV gamma rays of a 57Co flood source. The first appearing persistent focal accumulation is considered to be a sentinel node, especially when a direct connection from the injection site to the sentinel inguinofemoral node is visible. In accordance with local protocols a SPECT CT scan is made to detect the sentinel node.

On the day or the afternoon after the injection of the radioactive tracer, following induction of anaesthesia, ca. 0.5-1.0 ml of the blue dye (e.g. Patent blue-V (2.5% in aqueous solution containing 0.6% sodium chloride and 0.05% disodium hydrogen phosphate) is injected intradermal on the same 4 locations around the primary tumour approximately 5-10 minutes prior to the surgical procedure. The surgical procedure starts with identification and removal of the sentinel nodes. During surgery a handheld gamma-ray-detection probe is used to confirm the area of greatest activity in the groin. A small skin incision is made and a sentinel node excision biopsy is performed using the handheld gamma-ray detector and by dissection of blue-stained lymph vessels. Sentinel nodes are sent to the pathologist. Subsequently resection of the vulvar lesion is performed. When identification of the sentinel node is not successful because of low radioactivity, or by preference of the surgeon, the vulvar tumour is removed first. By resection of the vulvar tumour together with the primary Nano colloid injection sites the radiation background is greatly reduced, allowing easier identification of the sentinel nodes, especially when the primary tumour is near the groins. After removal of the sentinel nodes, the biopsy bed is re-examined for radioactivity, and if higher than 10% of the first excised lymph node, the dissection is continued in search of additional sentinel nodes.

5.1.4 Surgical protocol

Treatment consists of wide local excision of the vulvar tumour or a vulvectomy in combination with SLN procedure. All groins with a SLN on imaging should be explored; also when previously IFL was performed at that site. When sentinel nodes in one or two groins cannot be identified an inguinofemoral lymphadenectomy at either one or two sides should be performed, depending on the location of the tumour and consent of the patient. (Figures 2, 3 and 4) When preoperative imaging showed any enlarged groin node (shortest axis > 8 mm) this node should be removed.

5.1.5 Histopathology:

Macroscopy: the number of lymph nodes received should be described, as well as the size and macroscopic aspects of the lymph nodes. The lymph node should be cut in 2-3 mm slices, perpendicular to the long axis and then all slices should be embedded (do not embed different lymph nodes in the same block).

Microscopy: one routine H/E section (four mu) should be cut of all blocks and two unstained sections (do not cut deep into the block). If the sections are tumour negative step sections, 3 levels/mm (one section per 500 micro meter), should be cut. For the three sections at each level, one is stained with H/E, one is to be used for immunohistochemistry (cytokeratin AE1/AE3), while one spare section is preserved in case of technical difficulties with the IHC (include the first level for IHC). Metastases are defined as clusters of tumour cells of any size detected on haematoxylin and eosin slides or at immunohistochemistry, or isolated tumour cells detected at immunohistochemistry. Anucleate keratin-positive structures are not considered positive. The diameter of the sentinel node metastasis and presence of extranodal growth will be recorded.
Pathologic ultra-staging will only be performed on sentinel nodes and not on non-sentinel nodes as identified in full lymphadenectomy specimens.

Reporting: number of sentinel nodes. Number of lymph nodes in lymphadenectomy specimen. Number of nodes with metastatic involvement. Size of lymph node metastasis. Extra nodal tumour growth.

5.1.6 Additional surgery:

In case of a positive SLN on histology a full IFL is advised. However, local protocol might advise postoperative radiotherapy under certain circumstances.

5.1.7 Radiotherapy protocol

Standard (chemo) radiotherapy (see www.oncoline.nl for current standard treatment) is indicated postoperatively in case of more than 1 lymph node metastasis or in case of extracapsular tumour growth. Radiotherapy will include the inguinal and low pelvic lymph nodes. Radiotherapy should be initiated within 6 weeks after the final surgical procedure.

5.1.8 Follow-up

During the first 24 months follow-up will be done three-monthly: with physical examination including inspection and palpation of the groins and of the vulva, inspection of the legs (lymph oedema) and notification of the number of erysipelas episodes.
At months 6, and 12, and in case of suspected groin nodes, an ultrasound scan of the groins is requested. When ultrasonography shows enlarged or suspect lymph nodes, a FNA will be performed.
After 24 months the follow-up will be done in accordance with local protocols.

5.2 Use of co-intervention

Not applicable.

5.3 Escape medication

Not applicable.

6. INVESTIGATIONAL PRODUCT

Not applicable.

6.1 Name and description of investigational product(s)

Not applicable.

6.2 Summary of findings from non-clinical studies

Not applicable.

6.3 Summary of findings from clinical studies

Not applicable.

6.4 Summary of known and potential risks and benefits

Not applicable.

6.5 Description and justification of route of administration and dosage

Not applicable.

6.6 Dosages, dosage modifications and method of administration

Not applicable.

6.7 Preparation and labelling of Investigational Medicinal Product

Not applicable.

6.8 Drug accountability

Not applicable.

7. NON-INVESTIGATIONAL PRODUCT

Not applicable.

7.1 Name and description of investigational product(s)

Not applicable.

7.2 Summary of findings from non-clinical studies

Not applicable.

7.3 Summary of findings from clinical studies

Not applicable.

7.4 Summary of known and potential risks and benefits

Not applicable.

7.5 Description and justification of route of administration and dosage

Not applicable.

7.6 Dosages, dosage modifications and method of administration

Not applicable.

7.7 Preparation and labelling of Investigational Medicinal Product

Not applicable.

7.8 Drug accountability

Not applicable.

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study parameter/endpoint

The main study endpoint is the number of women who develop a groin recurrence within 24 months after a negative SLN procedure in 1st recurrent vulvar cancer. Clinical examination is done every 3 months, with an USS of the groin at 6 and 12 months. In case of suspicious findings FNA or histologic biopsy is performed.

8.1.2 Secondary study parameters/endpoints

Feasibility of the SLN procedure in recurrent vulvar cancer

This is the success rate of detection and retrieval of the sentinel node, both related to the percentage of women, as well as groins in whom the proposed SLN surgery is successfully performed.

Perioperative and postoperative morbidity and mortality

Data collection at 6 weeks after every surgery by the physician. Type of surgery (SLN right groin, SLN left groin, IFL right, IFL left, vulva surgery, reconstructive surgery). Location of SLN found (within IFL region or not), surgical challenges (unintended lesion of vena saphena magna, bleeding, others), duration of surgical procedure, complications (wound infections, wound breakdown, lymph oedema (see adverse effect Appendix 1)), length of hospital stay, re-surgery, readmission.

Incidence of tumour positive sentinel nodes

All specimen will be examined according to the protocol (See section 5.1.) depth of tumour infiltration, presence of LVSI, number of SLN's per groin, number of removed nodes per groin.

Adjuvant treatment

Adjuvant groin treatment; IFL, and or radiotherapy.

8.1.3 Other study parameters

Baseline data:

FIRST procedure: age at first procedure, localisation of tumour (medial / lateral), tumour size, depth of infiltration, LVSI, number of SLN right groin, number of SLN

left groin, IFL right site (number of lymph nodes), IFL left site (number of lymph nodes), previous radiotherapy, presence of LS or dysplasia, previous reconstructive surgery.

Interval between first surgical treatment and moment of relapse, guessed / estimated distance (cm) between original tumour and relapse, localisation of relapsed tumour, tumour size.
Intention to remove SLN ipsi- or bilateral, agreement on performing IFL in case SLN is not detected or retrieved.

Questionnaires

EQ-5D-5L. Standardized descriptive system of health-related quality of life states consisting of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) each of which can take one of five responses. The responses record five levels of severity (no problems/some problems/ moderate problems/severe problems/extreme problems) within a particular EQ-5D dimension. Besides the descriptive system, a standard vertical 20 cm visual analogue scale (similar to a thermometer) for recording an individual's rating for their current health-related quality of life state is part of the EQ-5D. It was developed by the EuroQol Group. (14, 15)

Decisional Conflict Scale (DCS). This scale measures: 1) health-care consumers' uncertainty in making a health-related decision; 2) the factors contributing to the uncertainty; and 3) health-care consumers' perceived effective decision making. Internal consistency coefficients range from 0.78 to 0.92. (16) This questionnaire will only be used at baseline.

Decision Regret Scale (DRS). The DRS is a 5-item scale and a useful indicator of health care decision regret at a given point in time. Internal consistency is good (Cronbach's alpha = 0.81 to 0.92). This questionnaire will be used to evaluate patient's decision 1 year after surgery. (17)

GCLQ7 questionnaire: This is a short version of the Gynaecologic Cancer Lymphedema Questionnaire. This questionnaire will be used at baseline, 6 and 12 months. (18)

8.2 Randomisation, blinding and treatment allocation

Not applicable.

8.3 Study procedures

Study Settings:
This study will be done within the existing partnership of the GROningen INternational Study on Sentinel nodes in Vulvar cancer (GROINSS-V) in hospitals that perform at least 20 SLNs yearly, and with experience of at least 5 SLN procedures in patients with recurrent V-SCC. In the first phase only the members of the writing committee will participate, all of them having experience with repeat SLN.(11) After 40 procedures other centres within the GROINSS-V consortium with similar experience can participate.

Preoperative dissemination:
Preoperative dissemination is performed by chest, abdominal and groin CT scanning. Ultrasound scanning of the groins is done, with fine needle aspiration of suspicious or enlarged nodes to rule out lymph node metastases.

For details on the *surgical procedure* see 5.1.3.

Questionnaires:
Questionnaires will be sent by the datacentre in Rotterdam, at baseline, 6 and 12 months, using e-mail with a link to web-based questionnaires. Sending and receiving questionnaires will be coordinated by a research nurse of the Erasmus MC. The participant should complete the web-based questionnaires by herself. The average time to complete questionnaires is approximately 15 – 30 minutes.
Participants are asked to complete questionnaires as much as possible at the indicated time points, but no more than one month sooner or later. In case participants are not able to receive or fill out web-based questionnaires, a paper version of the questionnaires will be sent with an answering envelop by the research nurse form the datacentre in Rotterdam. However, the use of web-based questionnaires is highly preferred.

Follow up:
Routine 3-montly clinical examination is combined with ultra-sonographic assessment of the groins at 6 and 12 months in women treated with the SLN procedure.

8.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

8.4.1 Specific criteria for withdrawal

Not applicable.

8.5 Replacement of individual subjects after withdrawal

Not applicable.

8.6 Follow-up of subjects withdrawn from treatment

Not applicable.

8.7 Premature termination of the study

The study will be terminated when the stopping rule is activated because of too many groin recurrences. See 4.4. sample size calculation for the stopping rules.

9. SAFETY REPORTING

9.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

9.2 AEs, SAEs and SUSARs

9.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to treatment. We will not report any adverse events.

9.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that:

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a serious adverse event.

The investigator will report death, life threatening events (at the time of the event) and the occurrence of groin recurrence to the sponsor without undue delay after obtaining knowledge of the events. The following SAEs: prolonged admittance or re-admittance to the hospital with problems like wound breakdown, urinary tract infections, wound infections, and erysipelas will only be reported at the end of the study, not in any annual safety report or otherwise since all are regular SAEs, related to the treatment and not related to the study.

The sponsor will report the SAEs death, life threatening events (at the time of the event) and the occurrence of groin recurrence through the web portal ToetsingOnline to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening or occurrence of a groin recurrence, followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will not be reported.

9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Not applicable.

9.3 Annual safety report

Groin recurrences and death of disease will be closely monitored. Safety reviews will be presented confidentially to the principal investigators every year. These annual reviews will include data on SAEs, number of deaths and cause of death, and number of groin recurrences. When the upper boundary of the stopping rule is passed all principal investigators will be informed immediately, and patient recruitment will instantaneously be paused. After interim safety analyses by the Safety Committee (see below) the study will be stopped, or continued, with or without adaptations.

9.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.
SAEs need to be reported till end of study within the Netherlands, as defined in the protocol.

9.5 Safety Committee

An independent Safety Committee will be appointed in case the stopping rule is activated to decide to definitively stop, or continue the study.
The Safety Committee will consist of an independent gynaecologic oncologist, an oncologic surgeon, an epidemiologist, (all three with experience in clinical trials and not entering patients in the study), a lay-person representing patients, and an independent biostatistician.

10. STATISTICAL ANALYSIS

Baseline data will be presented in a descriptive manner. Frequencies, relative frequencies, means and standard deviations will be calculated. To test for differences in baseline data, the Chi square and analysis for variance (ANOVA) are used for categorical and continuous variables respectively.
Statistical tests will be done two-sided and p-values are considered statistically significant when $p < 0.05$. Statistical analyses will be carried out using the statistical package SPSS for Windows (SPSS, Chicago, IL, USA).

10.1 Primary study parameter(s)

Groin recurrence after SLN

The main study endpoint is the number of women who develop a groin recurrence within 24 months after a technically successful SLN procedure in which the SLN was free from tumour in recurrent vulvar cancer. The prognosis (survival) is related to failure, whether uni- or bilateral, therefore the primary endpoint relates to patients rather than groins.
Women should have a full groin node dissection in case of technical problems (SLN does not appear on the scintigraphy, or cannot be retrieved at surgery). So to calculate SLN failure the women with a groin failure after IFL will not be considered as failure of the SLN procedure.
Women that refuse to consent for standard treatment, i.e., an IFL when the SLN is not feasible (Group B2) will only be included in the analyses of the primary outcome if the SLN is retrieved.
This failure is calculated by:
Total number of women with groin recurrence in a groin after tumour-negative SLN procedure divided by the number of women with successful uni- or bilateral SLN procedure * 100%.

10.2 Secondary study parameters/endpoints

Groin recurrence after IFL

When enough patients agree on the standard arm (Group A) we might be able to calculate the number of women who develop a groin recurrence within 24 months after a negative IFL procedure in 1st recurrent vulvar cancer.
This failure is calculated by:

Total number of women with groin recurrence in a groin after negative IFL procedure divided by the number of women with uni- or bilateral IFL procedure * 100%.

Feasibility of the SLN procedure in recurrent vulvar cancer.

This is the success rate of detection and retrieval of the sentinel node, both related to the number of women, as well as number of groins in whom the proposed SLN surgery is successfully performed. (Group B1-B2)

Prior to surgery the surgeon has to state what groin surgery should be done; ipsi or bilateral groin treatment and what treatment should be done in case the SLN is not visible, or not found during surgery (see section 5.1.2.).

Feasibility is calculated:

- in relation to participants / patients:

Total number of women with successful SLN procedure(s) as per preoperative defined protocol, divided by the number of women that undergo the SLN procedure * 100%

- per groins:

Total number of groins with successful SLN procedure (as per preoperative defined protocol), divided by the number of groins that should be treated with the SLN procedure * 100%

Unexpected SLN's

This consists of SLN's in groins previously treated with IFL and or radiotherapy and SLN's found at unpredicted place, beyond the border of the regular IFL treatment. (Group B1-B2)

- *SLN in groins previously treated with IFL and or radiotherapy*

- calculation of unexpected SLN's after previous IFL and or radiotherapy of the groin;

Total number of successful SLN's procedures in groins after previous IFL or radiotherapy of the groin, divided by total number of groins in whom a SLN was retrieved *100%.

- *SLN found at unpredicted places*

Total number of SLN's found at unpredicted places (outside the region of IFL), divided by total number of groins treated *100%.

- *Involvement of unexpected SLN's*

Total number of tumour positive unexpected SLN's, divided by total number of unexpected SLN's *100%.

Tumour positive SLN's

- as absolute number, and in relation to participants / patients:

Total number of women with uni or bilateral tumour positive SLNs, divided by the number of women with a successful SLN procedure * 100%.

- per groins:

Total number of groins with tumour positive SLNs, divided by the number of groins with successful SLN procedure * 100%.

Tumour positive groins

- in relation to participants / patients with groin surgery (pathology only):

Total number of women with uni or bilateral tumour positive lymph nodes, retrieved either by SLN or by IFL, divided by the number of women that underwent groin surgery * 100% (including women included in the non-SLN cohort, excluding women that did not have groin surgery in groups B2 C).

- in relation to participants / patients with first vulvar cancer recurrence:

Total number of women with uni or bilateral tumour positive lymph nodes, retrieved either by SLN or by IFL, and all women experiencing a groin recurrence during 24 month follow up, divided by the number of women included in the current study * 100% (including women included in the non-SLN cohort, and women that did not have groin surgery in group B2 and C).

- per groin:

Total number of tumour positive nodes divided by the number of groins treated *100%.

Outcome quality of life

QoL measurements will be done at baseline and 6, and 12 months after surgery. Linear description and comparison between standard treated and study arm treated patients will be performed. (Groups non SLN cohort, and A - C)

10.3 Other study parameters

Surgical complications

i.e., incidence of wound infections, wound breakdown, lymph oedema (see adverse effect Appendix 2) per patient and as absolute number. In relation to the previous

history and groin surgery performed, including all surgically treated patients (Groups non SLN cohort and A – C), comparing SLN treated groins with IFL treated groins.

Technical challenges

Description of unintended lesion of vena saphena magna, bleeding etc., duration of surgery to retrieve SLN. In relation to the previous history and groin surgery performed, including all surgically treated patients (Groups non SLN cohort and A – C), comparing SLN treated groins with IFL treated groins.

Patient's preferences

Standard treatment is uni- or bilateral IFL. In this study patients are offered SLN, with IFL when the SLN is not detected or retrieved. Preference for treatment is asked and noted in the file. The treating physician will note patients' preference in the application form. Patients will receive the Decisional Conflict Scale (DCS) and Decision Regret Scale (DRS). questionnaires regarding their treatment choices. (Group A – C) Decisions and regret scales will be compared between the groups (A – C) and related to patient characteristics like age, previous treatment and outcome like tumour positive groins and complications.

USS in follow up (Groups B1 - B2)

1) The number of suspicious USS in the follow up of women with negative LKT and SLN: USS with FNA, divided by the number of USS performed *100%.
2) Sensitivity and specificity of USS (with FNA) in women with negative LKT and SLN.
3) Protocol violation (USS not performed in women with negative LKT and SLN) divided by number of USS required in accordance with protocol *100%.

When a local or regional recurrence is diagnosed FU for this outcome stops.

Additional analyses

For the primary and secondary outcomes (failure of SLN and IFL procedure, feasibility, unexpected nodes, patients preferences, USS) univariate analyses will be done including the following parameters: tumour size, location, infiltration depth, treatment interval 1st and 2nd tumour, previous groin treatment, and age. Variables associated with ($P < 0.20$) in univariate analysis will be included in a multivariate logistic regression model. In the multivariate logistic and cox regression analyses, we only accepted ten events per variable to avoid overfitting (19).

The overall survival and progression free survival for the different groups (non SLN cohort and Groups A – C) will be described using the Kaplan-Meier analysis.
The overall survival (OS) is defined as the interval between the date of surgery for 1st recurrent vulvar cancer and the date of death or last visit/date last known to be alive.
Progression Free Survival (PFS) is defined as the interval between the date of surgery for 1st recurrent vulvar cancer and the date of documented disease progression, or last follow-up. Groin recurrence is censored in case of a 3rd local (vulvar) recurrence since any groin recurrence after such an event cannot be related to the 1st or 2nd recurrence. If a patient is lost to follow-up or dead because of unknown reason, she will be censored as of the date of last contact for the PFS.

10.4 Interim analysis

Interim analysis is not applicable; activation of the stopping rule can be any moment throughout the study period.

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (version10, October 2013, see for the most recent version: www.wma.net) and in accordance with the Medical Research Involving Human Subjects Act (WMO) and other guidelines, regulations and Acts.

11.2 Recruitment and consent

Patients will receive written and oral information on the study, by the treating gynaecologist. Written informed consent has to be obtained. Patients will have the opportunity to withdraw from the study at any time, will get at least a week to consider their participation in the study and will be notified in the patients' information sheet of the fact that they will have the opportunity to consult an independent physician, who is not involved in the study, for information and advice.

11.3 Objection by minors or incapacitated subjects

Not applicable.

11.4 Benefits and risks assessment, group relatedness

A full IFL is still the preferred treatment of recurrent vulvar cancer, but no comparison is made with SLN biopsy. However in breast cancer, repeat SLN is feasible and provides reliable results(12). There are no arguments why vulvar cancer should have different outcomes than breast cancer. It is possible that a SLN might increase the number of women with groin failure, opposed to standard IFL. However in our retrospective study, in 2 out of 27 patients, the SLN was located outside the surgical margins of the normal IFL, possibly due to an aberrant drainage pattern(11). So, the women with an aberrant pattern might benefit of the SLN procedure in case a positive SLN is found. Ultra-staging of the retrieved SLN might detect microscopic metastases that might have been unnoticed in IFL, and thereby improve the diagnostic (and may be clinical) outcome of affected women.
Since the majority of patients with recurrent vulvar cancer are frail, an observational study of accuracy, in which a SLN biopsy and an IFL are performed consecutively in one surgical procedure is not feasible: too many frail women will refuse this extensive surgery.

Since it is not guaranteed that a repeat SLN procedure is as safe as a primary SLN procedure, we have a stopping rule and a Safety Committee installed.

11.5 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO.
The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

11.6 Incentives

Not applicable.

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

The Central Datacentre is organized at the Erasmus MC and consists mainly of a study coordinator and research nurse. When the patient has signed the informed consent form, the treating physician will contact the Central Registration Centre for registration of this patient. (see appendix 2 for extensive details) The registration checklist should be filled out. After verifying that the patient meets all eligibility criteria and has signed the informed consent form, the patient can be registered. Each patient will be given a unique trial number. For privacy purposes, the patient will be registered by trial number. All further documents will be coded with this CRF number, making it impossible to directly relate data to individuals. The investigator must assure that the subject's anonymity will be maintained on all documents submitted to the Central Datacentre. To enable peer review and/or inspections from Health Authorities, the investigator must agree to keep records, including the identity of all participating subjects (sufficient information to link records, e.g. CRFs and hospital records), all original signed Informed Consent Forms, copies of all CRFs. To comply with international regulations, the investigator should retain the records for 15 years after study closure. The handling of personal data will comply with the General Data Protection Regulation (GDPR).

After written approval of the participant, the data and/or body tissues will be stored for a period of 20 years after study closure for future research purposes.

12.2 Monitoring and Quality Assurance

The Central Datacentre will perform extensive consistency checks on the CRFs and returned questionnaires in case of inconsistent data that will be sent to the investigator.

A study initiation meeting to fully inform the investigator of his/her responsibilities and the procedures for assuring adequate and correct documentation will be organized by the Study Coordinators.

The decision to perform monitoring visits on-site lies with the Study Coordinators, who may also decide who will perform the monitoring visits. Initial monitoring on informed consent, eligibility and safety will be performed by the study coordinator. All records will be maintained in accordance with local regulations and in a manner that ensures security and confidentiality.

Each subject will be identified in the CRF by a subject identification number. The subject identification number will be a sequential number.
Monitoring of data will be performed as described in Appendix B of the standard Erasmus MC monitoring plan.

12.3 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

12.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

12.5 Temporary halt and (prematurely) end of study report

The end of the study is reached when 125 patients have been successfully treated with a SLN procedure and completed two years of follow up, or earlier when the lower of upper border of the stopping rule are passed. The investigator/sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit.
The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.
In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination.
Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

12.6 Public disclosure and publication policy

All papers and abstracts will be co-authored by the study coordinators and by one investigator from each centre that has contributed one or more patients to the data to be analysed. Full articles on the clinical topics to the study will be prepared by the

study coordinator(s) and will also be co-authored by the statistician and possibly by the data manager. Presentations at national or international meetings may be given by investigators from individual centres, but will require the approval of the study coordinators prior to submission in all cases. These rules will apply exclusively to publications and/or presentations of data that have been collected among more than a single centre. Investigators remain free to report in any desired form on patients treated exclusively in their own centre.

This trial will be registered at *www.trialregister.nl/*

13. STRUCTURED RISK ANALYSIS

13.1 Potential issues of concern

Risk of groin recurrence: There is a risk that SLN procedure will not be as effective as full IFL. But there are sufficient data that support the feasibility of SLN in the first recurrence in vulvar cancer.
In breast cancer, repeat SLN is feasible and provides reliable results(12). There are no arguments why vulvar cancer should have different outcomes than breast cancer.
In our retrospective study, in 2 out of 27 patients, the SLN was located outside the surgical margins of the normal IFL, possibly due to an aberrant drainage pattern(11). These patients will not profit from a full IFL.
Since it is not guaranteed that a repeat SLN procedure is as safe as a primary SLN procedure, we have a stopping rule and a Safety Committee installed.

a. Level of knowledge about mechanism of action

Not applicable.

b. Previous exposure of human beings with the test product(s) and/or products with a similar biological mechanism

Not applicable.

c. Can the primary or secondary mechanism be induced in animals and/or in *ex-vivo* human cell material?

Not applicable.

d. Selectivity of the mechanism to target tissue in animals and/or human beings

Not applicable.

e. Analysis of potential effect

Not applicable.

f. Pharmacokinetic considerations

Not applicable.

g. Study population

Not applicable.

h. Interaction with other products

Not applicable.

i. Predictability of effect

Not applicable.

j. Can effects be managed?

Not applicable.

13.2 Synthesis

Since the majority of patients with recurrent vulvar cancer are frail, an observational study of accuracy, in which a SLN biopsy and an IFL are done during the same surgical procedure and in which the accuracy of the SLN is confirmed in the IFL is not feasible: too many frail women will refuse this extensive surgery.
In general, little information is available on groin recurrences and outcome of treatment in recurrent vulvar cancer. To reduce the knowledge gap we will ask all patients for either the non- SLN cohort (observational study) (in case an IFL is done because of a proven groin metastases) or the V2SLN study as described with the possibility for the patient to choose for a SLN procedure (or not).

14. REFERENCES

1. Meads C, Sutton A, Malysiak S, Kowalska M, Zapalska A, Rogozinska E, et al. Sentinel lymph node status in vulval cancer: systematic reviews of test accuracy and decision-analytic model-based economic evaluation. Health Technol Assess. 2013;17(60):1-216.
2. Charles FL, Shamshad A, Robert LC, Michael AG, Jeffrey MF, Patricia LJ, et al. Lymphatic Mapping and Sentinel Lymph Node Biopsy in Women With Squamous Cell Carcinoma of the Vulva: A Gynecologic Oncology Group Study. Journal of Clinical Oncology. 2012;30(31):3786-91.
3. Coleman RL, Ali S, Levenback CF, Gold MA, Fowler JM, Judson PL, et al. Is bilateral lymphadenectomy for midline squamous carcinoma of the vulva always necessary? An analysis from Gynecologic Oncology Group (GOG) 173. Gynecol Oncol. 2013;128(2):155-9.
4. Van der Zee AG, Oonk MH, De Hullu JA, Ansink AC, Vergote I, Verheijen RH, et al. Sentinel node dissection is safe in the treatment of early-stage vulvar cancer. J Clin Oncol. 2008;26(6):884-9.
5. A GJvdZ, M HO, Hullu JAD, Ansink AC, I.Vergote, Verheijen RH, et al. Sentinel Node Dissection Is Safe in the Treatment of Early-Stage Vulvar Cancer. Journal of Clinical Oncology. 2008;26(6):884-9.
6. Robison K, Roque D, McCourt C, Stuckey A, Disilvestro PA, Sung CJ, et al. Long-term follow-up of vulvar cancer patients evaluated with sentinel lymph node biopsy alone. Gynecol Oncol. 2014;133(3):416-20.
7. Te Grootenhuis NC, van der Zee AG, van Doorn HC, van der Velden J, Vergote I, Zanagnolo V, et al. Sentinel nodes in vulvar cancer: Long-term follow-up of the GROningen INternational Study on Sentinel nodes in Vulvar cancer (GROINSS-V) I. Gynecol Oncol. 2016;140(1):8-14.
8. Baiocchi G, Rocha RM. Vulvar cancer surgery. Current Opinion in Obstetrics and Gynecology. 2014;26(1):9-17.
9. Yap JK, Fox R, Leonard S, Ganesan R, Kehoe ST, Dawson CW, et al. Adjacent Lichen Sclerosis predicts local recurrence and second field tumour in women with vulvar squamous cell carcinoma. Gynecol Oncol. 2016;142(3):420-6.
10. Oonk MHM, de Hullu JA, van der Zee AJG. Letter to the Editor on “The Importance of Performing a Sentinel Node Biopsy in Case of Recurrent Vulvar Cancer”. International Journal of Gynecological Cancer. 2014;24(9):1537.
11. van Doorn HC, van Beekhuizen HJ, Gaarenstroom KN, van der Velden J, van der Zee AGJ, Oonk MHM, et al. Repeat sentinel lymph node procedure in patients with recurrent vulvar squamous cell carcinoma is feasible. Gynecologic Oncology. 2016;140(3):415-9.
12. Maaskant-Braat AJG, Roumen RMH, Voogd AC, Pijpers R, Luiten EJT, Rutgers EJT, et al. Sentinel Node and Recurrent Breast Cancer (SNARB): Results of a Nationwide Registration Study. Annals of Surgical Oncology. 2013;20(2):620-6.
13. Te Grootenhuis NC, Van Der Zee AGJ, Van Doorn HC, Van Der Velden J, Vergote I, Zanagnolo V, et al. Sentinel nodes in vulvar cancer: Long-term follow-up of the GROningen INternational Study on Sentinel nodes in Vulvar cancer (GROINSS-V) i. Gynecol Oncol. 2016;140(1):8-14.
14. EuroQol G. EuroQol--a new facility for the measurement of health-related quality of life. Health Policy. 1990;16(3):199-208.
15. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011;20(10):1727-36.
16. O'Connor AM. Validation of a decisional conflict scale. Med Decis Making. 1995;15(1):25-30.
17. Brehaut JC, O'Connor AM, Wood TJ, Hack TF, Siminoff L, Gordon E, et al. Validation of a decision regret scale. Med Decis Making. 2003;23(4):281-92.
18. Kim SI, Kim N, Lee S, Lee S, Joo J, Seo SS, et al. Development of the short version of the Gynecologic Cancer Lymphedema Questionnaire: GCLQ-7. J Gynecol Oncol. 2017;28(2):e9.
19. Vittinghoff E, McCulloch CE. Relaxing the rule of ten events per variable in logistic and Cox regression. Am J Epidemiol. 2007;165(6):710-8.
20. Lee JJ, Liu DD. A predictive probability design for phase II cancer clinical trials. Clin Trials. 2008;5(2):93-106.

Appendix 1: Stopping rules

The predictive probability design for phase II cancer clinical trial as described by Lee and Liu was used to develop the stopping rule for this study. (20)This method has the advantage over two and three stage designs that the safety can be monitored constantly rather than at a pre-specified fixed number of patients.

Under the hypothesis testing framework, this clinical trial is designed to test
H0 : $p \leq p_0$
against
H1 : $p \geq p_1$
where p represents the success rate of the SLN procedure, so that $1 - p$ is the failure rate. p_1 is the target success rate and p_0 is the minimally acceptable success rate. We consider a failure rate of SLN of 8% (i.e. $1 - p_1$) to be maximally acceptable, and our target failure rate (i.e. $1 - p_0$) is 3%. The study is designed such that P(Accept New Treatment|H0) ≤ α, and P (Reject New Treatment|H1) ≤β, where the maximum type I error α and the maximum type II error rate β are both set to 0.10.

In this model, we calculate PP continuously after 10 patients (i.e., with cohort size of 1) to monitor the treatment safety.

The stopping rule is based on the predictive probability (PP) of concluding a positive result by the end of the trial based on the cumulative information in the current stage. In this model, we calculate PP continuously after 10 patients (i.e., with cohort size of 1) to monitor the treatment safety. The trial is stopped when the PP drops below the lower bound ϑ_l, where ϑ_l is a parameter that is optimized by the method. The method of Lee and Liu also includes an option for early stopping of the trial in case the PP is very close to 1, using an upper bound ϑ_u. However, we did not utilize this option, since we do not expect to have to stop the trial in case the SLN procedure has a lower groins failure rate than IFL.

In the Bayesian predictive probability approach, we assume that the failure rate ($1 - p$) has a prior distribution of Beta (0.2; 0.8), which has a prior mean of 20%. Using the software of Lee and Liu (see
https://biostatistics.mdanderson.org/SoftwareDownload/SingleSoftware/Index/84) we calculated the minimum number of patients to obtain sufficient power with acceptable type I error rate using a ‘max power’ approach. The results gave a sample size of 150 patients, with

a threshold for stopping the trial of $\vartheta_l = 0.001$. The full output of the program is given below, and Figure 3 shows the stopping rule graphically.

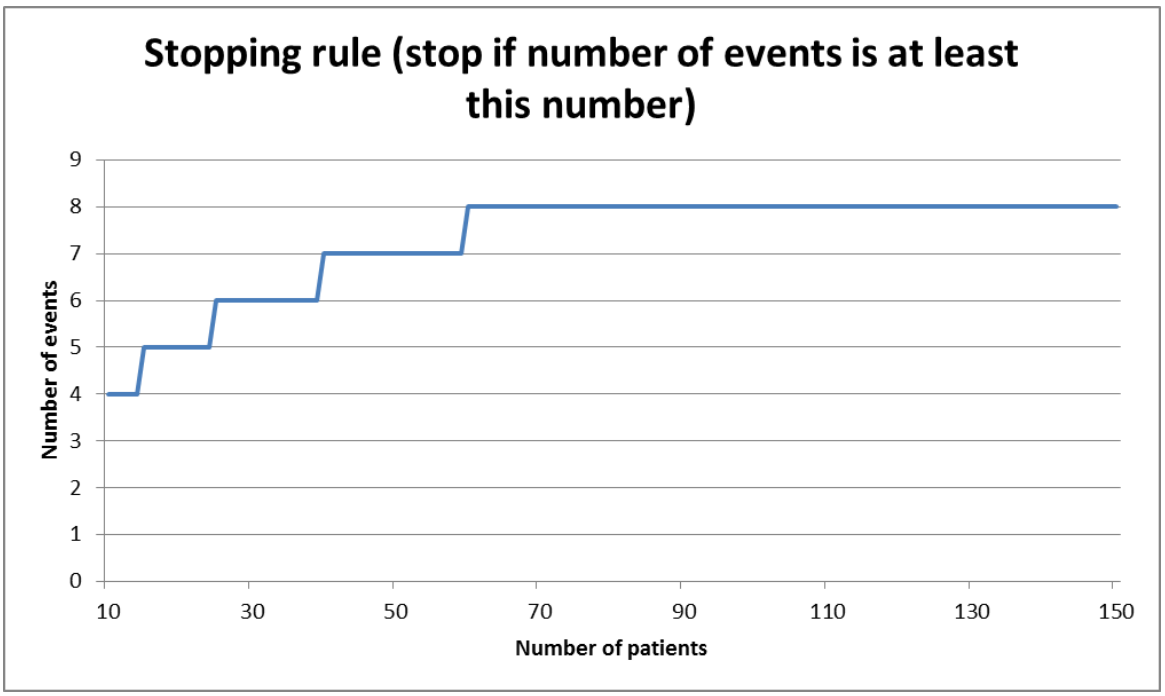


Figure 3 Activation of stopping rule; number of groin recurrences in relation to patients with negative SLN

Program output

Input Data

==========

10	Nmin
1	Cohort
150	Nmax
0.0010	theta_Lbegin
0.1000	theta_Lend
0.0050	theta_Lstep
1.0000	theta_Upper
0.8000	theta_Tbegin
0.9500	theta_Tend
0.0100	theta_Tstep
0.9200	p_0
0.9700	p_1
0.8000	Prior a0
0.2000	Prior b0
0.1000	Type I Error
0.9000	Power

Calculation Result

==========

Parameter selection: Maximize Power.
Theta_L and theta_T ranges:
Theta_L 0.0010 0.0010
Theta_T 0.9100 0.9500

Null Case

==========

Pat.No.	Rej. Reg. (Negative)	Rej. Reg. (Positive)	Prob./(p0) (Negative)	Prob./(p0) (Positive)	Prob. Cont./(p0)
10	6	11	0.0058	0.0000	0.9942
11	7	12	0.0027	0.0000	0.9915
12	8	13	0.0035	0.0000	0.9880
13	9	14	0.0043	0.0000	0.9837
14	10	15	0.0051	0.0000	0.9786
15	10	16	0.0000	0.0000	0.9786
16	11	17	0.0005	0.0000	0.9782
17	12	18	0.0010	0.0000	0.9772
18	13	19	0.0015	0.0000	0.9757
19	14	20	0.0021	0.0000	0.9736
20	15	21	0.0027	0.0000	0.9709
21	16	22	0.0033	0.0000	0.9675
22	17	23	0.0040	0.0000	0.9636
23	18	24	0.0046	0.0000	0.9590
24	19	25	0.0053	0.0000	0.9537
25	19	26	0.0000	0.0000	0.9537
26	20	27	0.0005	0.0000	0.9532
27	21	28	0.0010	0.0000	0.9522
28	22	29	0.0015	0.0000	0.9508
29	23	30	0.0020	0.0000	0.9488
30	24	31	0.0025	0.0000	0.9463
31	25	32	0.0031	0.0000	0.9432
32	26	33	0.0036	0.0000	0.9396
33	27	34	0.0042	0.0000	0.9354
34	28	35	0.0047	0.0000	0.9307
35	29	36	0.0053	0.0000	0.9254
36	30	37	0.0058	0.0000	0.9196
37	31	38	0.0064	0.0000	0.9132
38	32	39	0.0069	0.0000	0.9063
39	33	40	0.0075	0.0000	0.8989
40	33	41	0.0000	0.0000	0.8989
41	34	42	0.0006	0.0000	0.8982
42	35	43	0.0013	0.0000	0.8969
43	36	44	0.0019	0.0000	0.8951
44	37	45	0.0025	0.0000	0.8926
45	38	46	0.0031	0.0000	0.8895
46	39	47	0.0037	0.0000	0.8858
47	40	48	0.0042	0.0000	0.8816
48	41	49	0.0048	0.0000	0.8768
49	42	50	0.0053	0.0000	0.8714
50	43	51	0.0059	0.0000	0.8656
51	44	52	0.0064	0.0000	0.8592

52	45	53	0.0069	0.0000	0.8523
53	46	54	0.0074	0.0000	0.8449
54	47	55	0.0078	0.0000	0.8371
55	48	56	0.0083	0.0000	0.8288
56	49	57	0.0087	0.0000	0.8201
57	50	58	0.0091	0.0000	0.8110
58	51	59	0.0095	0.0000	0.8015
59	52	60	0.0099	0.0000	0.7916
60	52	61	0.0000	0.0000	0.7916
61	53	62	0.0008	0.0000	0.7908
62	54	63	0.0016	0.0000	0.7892
63	55	64	0.0023	0.0000	0.7869
64	56	65	0.0030	0.0000	0.7838
65	57	66	0.0037	0.0000	0.7801
66	58	67	0.0043	0.0000	0.7758
67	59	68	0.0049	0.0000	0.7708
68	60	69	0.0055	0.0000	0.7653
69	61	70	0.0061	0.0000	0.7593
70	62	71	0.0066	0.0000	0.7527
71	63	72	0.0070	0.0000	0.7457
72	64	73	0.0075	0.0000	0.7382
73	65	74	0.0079	0.0000	0.7302
74	66	75	0.0083	0.0000	0.7219
75	67	76	0.0087	0.0000	0.7132
76	68	77	0.0090	0.0000	0.7042
77	69	78	0.0093	0.0000	0.6949
78	70	79	0.0096	0.0000	0.6852
79	71	80	0.0099	0.0000	0.6753
80	72	81	0.0102	0.0000	0.6652
81	73	82	0.0104	0.0000	0.6548
82	74	83	0.0106	0.0000	0.6442
83	75	84	0.0108	0.0000	0.6335
84	76	85	0.0109	0.0000	0.6226
85	77	86	0.0111	0.0000	0.6115
86	78	87	0.0112	0.0000	0.6003
87	79	88	0.0113	0.0000	0.5891
88	80	89	0.0114	0.0000	0.5777
89	81	90	0.0114	0.0000	0.5663
90	82	91	0.0115	0.0000	0.5548
91	83	92	0.0115	0.0000	0.5433
92	84	93	0.0115	0.0000	0.5318
93	85	94	0.0115	0.0000	0.5202
94	86	95	0.0115	0.0000	0.5087
95	87	96	0.0115	0.0000	0.4972
96	88	97	0.0114	0.0000	0.4858
97	89	98	0.0114	0.0000	0.4744
98	90	99	0.0113	0.0000	0.4631
99	91	100	0.0113	0.0000	0.4518
100	92	101	0.0112	0.0000	0.4406
101	93	102	0.0111	0.0000	0.4296
102	94	103	0.0110	0.0000	0.4186
103	95	104	0.0109	0.0000	0.4077
104	96	105	0.0107	0.0000	0.3970
105	97	106	0.0106	0.0000	0.3863

106	98	107	0.0105	0.0000	0.3759
107	99	108	0.0103	0.0000	0.3655
108	100	109	0.0102	0.0000	0.3553
109	101	110	0.0100	0.0000	0.3453
110	102	111	0.0099	0.0000	0.3354
111	103	112	0.0097	0.0000	0.3257
112	104	113	0.0096	0.0000	0.3161
113	105	114	0.0094	0.0000	0.3067
114	106	115	0.0092	0.0000	0.2975
115	107	116	0.0090	0.0000	0.2884
116	108	117	0.0089	0.0000	0.2796
117	109	118	0.0087	0.0000	0.2709
118	110	119	0.0085	0.0000	0.2624
119	111	120	0.0083	0.0000	0.2540
120	112	121	0.0081	0.0000	0.2459
121	113	122	0.0080	0.0000	0.2379
122	114	123	0.0078	0.0000	0.2301
123	115	124	0.0076	0.0000	0.2225
124	116	125	0.0074	0.0000	0.2151
125	117	126	0.0072	0.0000	0.2079
126	118	127	0.0071	0.0000	0.2008
127	119	128	0.0069	0.0000	0.1939
128	120	129	0.0067	0.0000	0.1872
129	121	130	0.0065	0.0000	0.1807
130	122	131	0.0063	0.0000	0.1744
131	123	132	0.0062	0.0000	0.1682
132	124	133	0.0060	0.0000	0.1622
133	125	134	0.0058	0.0000	0.1563
134	126	135	0.0057	0.0000	0.1507
135	127	136	0.0055	0.0000	0.1452
136	128	137	0.0053	0.0000	0.1398
137	129	138	0.0052	0.0000	0.1346
138	130	139	0.0050	0.0000	0.1296
139	131	140	0.0049	0.0000	0.1247
140	132	141	0.0047	0.0000	0.1200
141	133	142	0.0046	0.0000	0.1154
142	134	143	0.0044	0.0000	0.1110
143	135	144	0.0043	0.0000	0.1067
144	136	145	0.0041	0.0000	0.1026
145	137	146	0.0040	0.0000	0.0986
146	138	147	0.0039	0.0000	0.0947
147	139	148	0.0037	0.0000	0.0909
148	140	149	0.0036	0.0000	0.0873
149	141	150	0.0035	0.0000	0.0838
150	142	151	0.0034	0.0805	0.0000

==========

Sum: 0.9195 0.0805

PET (PP<Theta_L)/(p0): 0.9162
PET (PP>Theta_U)/(p0): 0.0000
PET Total /(p0): 0.9162
E(N|p0): 93.4786

Alternative Case

Pat.No.	Rej. Reg. (Negative)	Rej. Reg. (Positive)	Prob./(p1) (Negative)	Prob./(p1) (Positive)	Prob. Cont./(p0)
10	6	11	0.0001	0.0000	0.9999
11	7	12	0.0001	0.0000	0.9998
12	8	13	0.0001	0.0000	0.9997
13	9	14	0.0001	0.0000	0.9995
14	10	15	0.0002	0.0000	0.9994
15	10	16	0.0000	0.0000	0.9994
16	11	17	0.0000	0.0000	0.9994
17	12	18	0.0000	0.0000	0.9993
18	13	19	0.0000	0.0000	0.9993
19	14	20	0.0000	0.0000	0.9993
20	15	21	0.0000	0.0000	0.9992
21	16	22	0.0001	0.0000	0.9992
22	17	23	0.0001	0.0000	0.9991
23	18	24	0.0001	0.0000	0.9990
24	19	25	0.0001	0.0000	0.9989
25	19	26	0.0000	0.0000	0.9989
26	20	27	0.0000	0.0000	0.9989
27	21	28	0.0000	0.0000	0.9989
28	22	29	0.0000	0.0000	0.9989
29	23	30	0.0000	0.0000	0.9989
30	24	31	0.0000	0.0000	0.9988
31	25	32	0.0000	0.0000	0.9988
32	26	33	0.0000	0.0000	0.9988
33	27	34	0.0000	0.0000	0.9987
34	28	35	0.0001	0.0000	0.9987
35	29	36	0.0001	0.0000	0.9986
36	30	37	0.0001	0.0000	0.9985
37	31	38	0.0001	0.0000	0.9984
38	32	39	0.0001	0.0000	0.9983
39	33	40	0.0001	0.0000	0.9982
40	33	41	0.0000	0.0000	0.9982
41	34	42	0.0000	0.0000	0.9982
42	35	43	0.0000	0.0000	0.9982
43	36	44	0.0000	0.0000	0.9982
44	37	45	0.0000	0.0000	0.9982
45	38	46	0.0000	0.0000	0.9981
46	39	47	0.0000	0.0000	0.9981
47	40	48	0.0000	0.0000	0.9981
48	41	49	0.0000	0.0000	0.9980
49	42	50	0.0001	0.0000	0.9980
50	43	51	0.0001	0.0000	0.9979
51	44	52	0.0001	0.0000	0.9979
52	45	53	0.0001	0.0000	0.9978
53	46	54	0.0001	0.0000	0.9977
54	47	55	0.0001	0.0000	0.9976
55	48	56	0.0001	0.0000	0.9975
56	49	57	0.0001	0.0000	0.9974
57	50	58	0.0001	0.0000	0.9972
58	51	59	0.0001	0.0000	0.9971
59	52	60	0.0002	0.0000	0.9969

60	52	61	0.0000	0.0000	0.9969
61	53	62	0.0000	0.0000	0.9969
62	54	63	0.0000	0.0000	0.9969
63	55	64	0.0000	0.0000	0.9969
64	56	65	0.0000	0.0000	0.9969
65	57	66	0.0000	0.0000	0.9968
66	58	67	0.0000	0.0000	0.9968
67	59	68	0.0000	0.0000	0.9967
68	60	69	0.0001	0.0000	0.9967
69	61	70	0.0001	0.0000	0.9966
70	62	71	0.0001	0.0000	0.9966
71	63	72	0.0001	0.0000	0.9965
72	64	73	0.0001	0.0000	0.9964
73	65	74	0.0001	0.0000	0.9963
74	66	75	0.0001	0.0000	0.9962
75	67	76	0.0001	0.0000	0.9961
76	68	77	0.0001	0.0000	0.9960
77	69	78	0.0001	0.0000	0.9958
78	70	79	0.0002	0.0000	0.9957
79	71	80	0.0002	0.0000	0.9955
80	72	81	0.0002	0.0000	0.9953
81	73	82	0.0002	0.0000	0.9951
82	74	83	0.0002	0.0000	0.9949
83	75	84	0.0002	0.0000	0.9947
84	76	85	0.0002	0.0000	0.9945
85	77	86	0.0003	0.0000	0.9942
86	78	87	0.0003	0.0000	0.9939
87	79	88	0.0003	0.0000	0.9936
88	80	89	0.0003	0.0000	0.9933
89	81	90	0.0003	0.0000	0.9930
90	82	91	0.0003	0.0000	0.9927
91	83	92	0.0004	0.0000	0.9923
92	84	93	0.0004	0.0000	0.9919
93	85	94	0.0004	0.0000	0.9915
94	86	95	0.0004	0.0000	0.9911
95	87	96	0.0004	0.0000	0.9906
96	88	97	0.0005	0.0000	0.9902
97	89	98	0.0005	0.0000	0.9897
98	90	99	0.0005	0.0000	0.9892
99	91	100	0.0005	0.0000	0.9886
100	92	101	0.0006	0.0000	0.9880
101	93	102	0.0006	0.0000	0.9874
102	94	103	0.0006	0.0000	0.9868
103	95	104	0.0006	0.0000	0.9862
104	96	105	0.0007	0.0000	0.9855
105	97	106	0.0007	0.0000	0.9848
106	98	107	0.0007	0.0000	0.9841
107	99	108	0.0008	0.0000	0.9833
108	100	109	0.0008	0.0000	0.9825
109	101	110	0.0008	0.0000	0.9817
110	102	111	0.0009	0.0000	0.9808
111	103	112	0.0009	0.0000	0.9799
112	104	113	0.0009	0.0000	0.9790
113	105	114	0.0010	0.0000	0.9781

114	106	115	0.0010	0.0000	0.9771
115	107	116	0.0010	0.0000	0.9761
116	108	117	0.0011	0.0000	0.9750
117	109	118	0.0011	0.0000	0.9739
118	110	119	0.0011	0.0000	0.9728
119	111	120	0.0012	0.0000	0.9716
120	112	121	0.0012	0.0000	0.9704
121	113	122	0.0012	0.0000	0.9692
122	114	123	0.0013	0.0000	0.9679
123	115	124	0.0013	0.0000	0.9666
124	116	125	0.0013	0.0000	0.9653
125	117	126	0.0014	0.0000	0.9639
126	118	127	0.0014	0.0000	0.9625
127	119	128	0.0015	0.0000	0.9610
128	120	129	0.0015	0.0000	0.9595
129	121	130	0.0015	0.0000	0.9580
130	122	131	0.0016	0.0000	0.9564
131	123	132	0.0016	0.0000	0.9548
132	124	133	0.0017	0.0000	0.9531
133	125	134	0.0017	0.0000	0.9514
134	126	135	0.0017	0.0000	0.9497
135	127	136	0.0018	0.0000	0.9479
136	128	137	0.0018	0.0000	0.9461
137	129	138	0.0019	0.0000	0.9442
138	130	139	0.0019	0.0000	0.9423
139	131	140	0.0020	0.0000	0.9403
140	132	141	0.0020	0.0000	0.9383
141	133	142	0.0020	0.0000	0.9363
142	134	143	0.0021	0.0000	0.9342
143	135	144	0.0021	0.0000	0.9321
144	136	145	0.0022	0.0000	0.9299
145	137	146	0.0022	0.0000	0.9277
146	138	147	0.0023	0.0000	0.9255
147	139	148	0.0023	0.0000	0.9232
148	140	149	0.0023	0.0000	0.9208
149	141	150	0.0024	0.0000	0.9184
150	142	151	0.0024	0.9160	0.0000
Sum:			0.0840	0.9160	

PET (PP<Theta_L)/(p1): 0.0816
PET (PP>Theta_U)/(p1): 0.0000
PET Total /(p1): 0.0816
E(N|p1): 147.7381

Alpha: 0.0805
Beta: 0.0840

Predictive Probability Program PID-535
8/7/2019 6:18:48 PM

Appendix 2: Surgical flowcharts

A. Surgery of the ipsilateral groin in case a tumour is situated > 1 cm from the midline

Any SLN showing on the scintigram in the *contralateral* groin is removed, regardless previous treatment. When the SLN fails, further treatment is not warranted.

In the middle previous treatment of the *ipsilateral* groin.

At the right hand site treatment of *ipsilateral* groin.

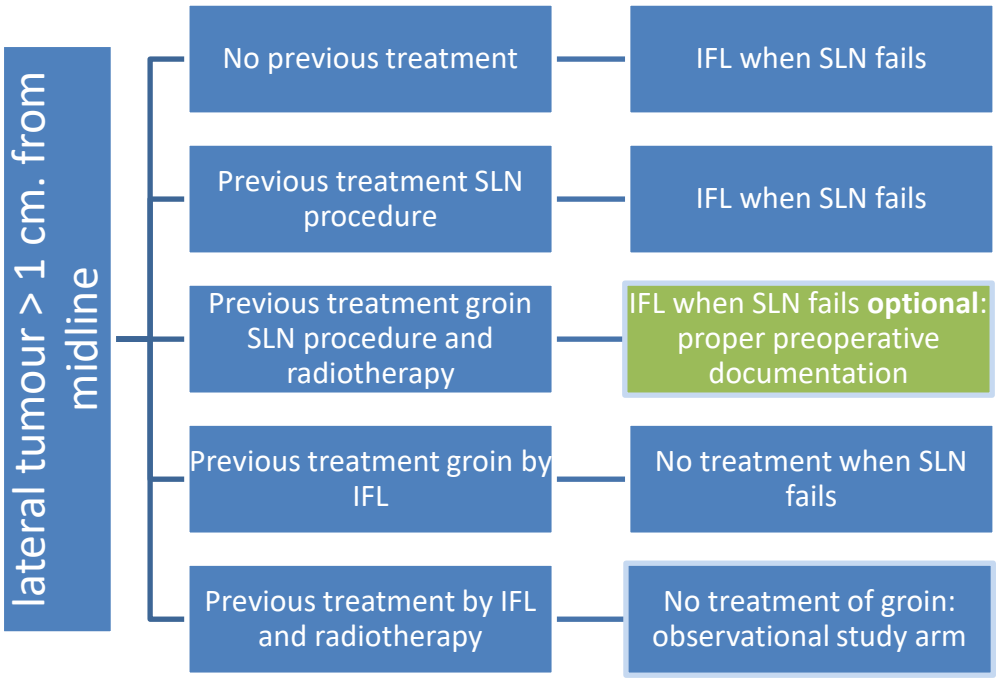


Figure 5 Surgery of the ipsilateral groin in case a tumour is situated > 1 cm from the midline

B Surgery in case a tumour is within 1 cm from the midline, without crossing the midline

Any SLN showing on the scintigram in the *contralateral* groin is removed, regardless previous treatment.

In the middle previous treatment of the groins

At the right hand site treatment of ipsilateral groin.

Green boxes to be discussed with the patients and decision documented in the chart

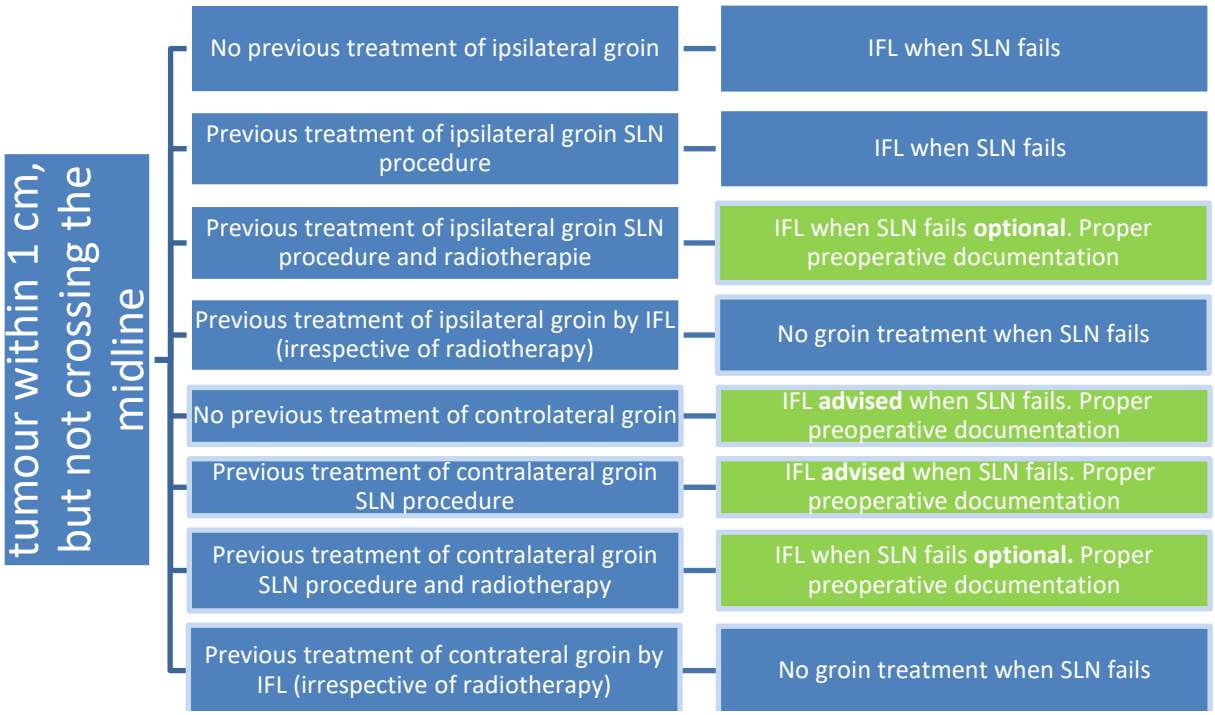


Figure 6 Surgery in case a tumour is within 1 cm from the midline, without crossing the midline

C Surgery in case a tumour crosses the midline

The schedule applies for both groins.

In the middle previous treatment per groin.

At the right hand site treatment per groin.

(*) in case of previous bilateral IFL with radiotherapy the patients should be consented for the non- SLN cohort study.

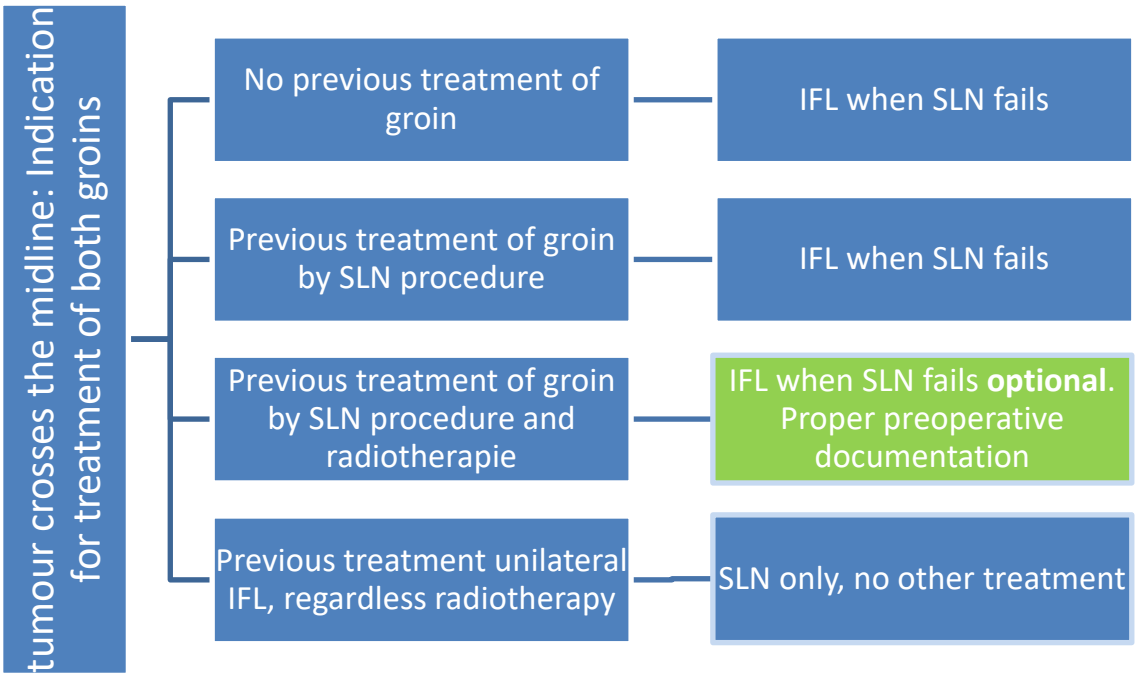


Figure 7 Surgery in case a tumour crosses the midline

Appendix 3: CTCAE criteria

Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 Published: May 28, 2009 (v4.03: June 14, 2010) (https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf)

			Grade		
Adverse Event	1	2	3	4	5
Infections and infestations					
Urinary tract infection Definition: A disorder characterized by an infectious process involving the urinary tract, most commonly the urethra and bladder.	-	Localized: *local intervention indicated* (e.g., topical antibiotics, antifungal or antiviral)	IV antibiotics, antifungal or antiviral intervention indicated: radiologoc or operative intervention indicated	Life-threatening consequences: urgent intervention indicated	Death
Skin infection Definition: A disorder characterized by an infectious process involving the skin	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences: urgent intervention indicated	Death
Wound infection: Definition: A disorder characterized by an infectious process involving the wound.	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences: urgent intervention indicated	Death
Vascular disorders					
Lymphedema Definition: A disorder characterized by excessive fluid	Trace thickening or faint discoloration	Marked discoloration; leathery skin texture; papillary formation;	Severe symptoms; limiting self care ADL		

collection in tissues that causes swelling		limiting instrumental ADL			
Lymphocele Definition: A disorder characterized by a cystic lesion containing lymph	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated		

Appendix 4: Procedures and forms data collection.

Patient's registration will only be accepted from authorized investigators.

Patients should sign informed consent prior to registry.

Overview of the forms and additional documents to be collected:

Form	Name	When	Additional documents
A	ELIGIBILITY FORM (A)	Registration	
B	DECISION ON TREATMENT FORM (B)	Registration	
C	PRIMARY TUMOUR & LYMPH NODES FORM (C)		Photograph when (still) available
D1	CURRENT TUMOUR & LYMPH NODES FORM (D1)		Photograph with ruler
D2	PRE OPERATIVE IMAGING FORM-ULTRASOUND- (D2)		Copy of imaging report CoIR)
D3	PRE OPERATIVE IMAGING FORM-CT- (D3)		CoIR
D4	PREOPERATIVE IMAGING FORM –MRI- (D4)		CoIR
E	TUMOUR SURGERY TREATMENT FORM (E)		Surgical notes
F	SENTINEL NODES SURGERY FORM (F)		Surgical notes
G	POSTOPERATIVE PERIOD FORM (G)		
H	PATHOLOGY REPORT FORM (H)	After surgery	Original pathology report
J	ADDITIONAL TREATMENT FORM (J)		
K	FOLLOW UP FORM 3 MONTHS AFTER COMPLETION OF TREATMENT(k)		
L	FOLLOW UP FORM 6 MONTHS AFTER COMPLETION OF TREATMENT: clinical assessment (L)		
M	FOLLOW UP FORM 6 MONTHS AFTER COMPLETION OF TREATMENT: Ultasound scan(M)	6m	CoIR
N	FOLLOW UP FORM 9 MONTHS AFTER COMPLETION OF TREATMENT(N)		
O	FOLLOW UP FORM 12 MONTH AFTER COMPLETION OF TREATMENT clinical assessment(O)		
P	FOLLOW UP FORM 12 MONTHS AFTER COMPLETION OF TREATMENT ultrasound scan (P)	12 m	CoIR

Q	FOLLOW UP FORM 15 MONTHS AFTER COMPLETION OF TREATMENT(Q)		
R	FOLLOW UP FORM 18 MONTHS AFTER COMPLETION OF TREATMENT(R)		
S	FOLLOW UP FORM 21 MONTHS AFTER COMPLETION OF TREATMENT(S)		
T	FOLLOW UP FORM 24 MONTHS AFTER COMPLETION OF TREATMENT(T)	24 m	

Patients must be registered prior to surgery. A patient can be registered after verification of eligibility: Form A (eligibility form).
At registration, before surgery Form B (planned surgery) should be completed to minimalize bias.
At the end of the registration procedure, a number will be allocated to the patient (patient sequential study number) send by the study secretariat by fax or email.
The study identification number attributed to the patient at the end of the registration procedure identifies the patient and must be reported on all case forms.

After surgery additional treatment is given, or the observational study starts.

Patient data will be collected in standard case report forms with NCR (non-carbon required) paper or through an electronic database.
Patient data are only available to the principal investigators at each participating institution.
CRFs must be completed and signed by the investigator as soon as the requested information is available, according to the schedule (see below). It is the responsibility of the investigator to check that all original CRFs have been sent to the Study secretariat and that they are completely and correctly filled out. The original CRF papers must be sent to the study secretary, the copies of the NCR papers remain in the study centre.
Data, as collected in the CRF will be sent to the study-secretary
V2SLN studie, Dr H. C. van Doorn
Erasmus MC Cancer Institute
Department of Gynaecological Oncology
Room Na15-03
Antwoordnummer 55
3000 WB Rotterdam
Email: V2SLN@erasmusmc.nl

CRFs must be completed according to the following schedule:

1. Registration: Before treatment starts send eligibility form (A) and decision on treatment Form (B) to the study secretariat The study secretariat will return a patient sequential identification number.
2. After completion of surgical treatment Form C-H, an image of the tumour, with a cm marker, and the corresponding copies of the Pathology Report(s) copies, imaging reports and surgical notes.
3. In case of additional treatment Forms J as soon as possible, but no later than at 6 months.
4. At 6 months after treatment Form J – M.
5. At 12 months after treatment Form N – P.
6. At 24 months after treatment Form Q - T.

When a groin recurrence, or death occurs and has been confirmed by pathology, the study coordinator and/or study secretary will be notified immediately. The study coordinator will determine whether the stopping rule has to be activated.

Appendix 5: Participating centres

Participating centres	PI	Study centres number
University Medical Center Groningen	M Oonk	100
Academic Medical Center Amsterdam	G Fons	200
Erasmus MC, Rotterdam	HC van Doorn	400
Leiden University Medical Center	KN Gaarenstroom	600
RadboudUMC	JA de Hullu	700

Appendix 6: Questionnaires

	EQ-5D-5L. baseline. 6 and 12 months	Adjusted GCLQ baseline, 6 and 12 months	Decisional Conflict Scale (DCS). baseline.	Decision Regret Scale (DRS). 1 year after surgery.
Non- SLN cohort	X	X		
V2SLN Group A	X	X	X	X
V2SLN Group B1	X	X	X	X
V2SLN Group B2	X	X	X	X
V2SLN Group C	X	X	X	X

EQ-5D-5L

Zet bij iedere groep in de lijst hieronder een kruisje in het hokje achter de zin die het best past bij uw eigen gezondheidstoestand vandaag.

Mobiliteit

Ik heb geen problemen met lopen ☐

Ik heb enige problemen met lopen ☐

Ik ben bedlegerig ☐

Zelfzorg

Ik heb geen problemen om mijzelf te wassen of aan te kleden ☐

Ik heb enige problemen om mijzelf te wassen of aan te kleden ☐

Ik ben niet in staat mijzelf te wassen of aan te kleden ☐

Dagelijkse activiteiten (bijv. werk, studie, huishouden, gezins- en vrijetijdsactiviteiten)

Ik heb geen problemen met mijn dagelijkse activiteiten ☐

Ik heb enige problemen met mijn dagelijkse activiteiten ☐

Ik ben niet in staat mijn dagelijkse activiteiten uit te voeren ☐

Pijn/klachten

Ik heb geen pijn of andere klachten ☐

Ik heb matige pijn of andere klachten ☐

Ik heb zeer ernstige pijn of andere klachten ☐

Stemming

Ik ben niet angstig of somber ☐

Ik ben matig angstig of somber ☐

Ik ben erg angstig of somber ☐

Adjusted GCLQ

Please check one answer per line.

1. Do you have limited movement of your knee? Yes □ No □

8. Have you experienced swelling of your foot, leg, hip, groin or your lower body in the past 4 weeks? Yes □ No □

10. Have you experienced redness of your foot, leg, hip, groin or your lower body in the past 4 weeks? Yes □ No □

12. Have you experienced firmness/tightness? Yes □ No □

14. Have you experienced heaviness of the legs? Yes □ No □

17. Have you experienced aching in de benen? Yes □ No □

19. Have you experienced groin swelling? (genital, labia/vulvar) Yes □ No □

In Nederlands:

De volgende vragen hebben betrekking op klachten die u zou kunnen hebben van uw voeten, benen, heup, lies of onderlichaam in de afgelopen 4 weken:

Had u last van zwelling van de weefsels in het genoemde gebied? Ja □ Nee □

Had u last van roodheid in het genoemde gebied? Ja □ Nee □

Had u last van een gespannen beklemmend of vast gevoel in het genoemde gebied? Ja □ Nee □

Had u pijn in het genoemde gebied? Ja □ Nee □

Had u last van een zwaar gevoel in de benen? Ja □ Nee □

Had u last van een zwelling van uw lies, en of in de schaamstreek? Ja □ Nee □

Had u last van verminderde bewegelijkheid van uw knie? Ja □ Nee □

Decision Conflict Scale

De volgende stellingen gaan over de beslissing die u hebt gemaakt over welke operatie u zal ondergaan. Kunt u aangeven in hoeverre u het eens bent met deze stellingen? De antwoorden worden gegeven op een 5-punts schaal van helemaal mee eens tot helemaal mee oneens.

	Onzekerheid over de beslissing
1.	Ik vind/vond het moeilijk om deze beslissing te nemen Helemaal mee eens ☐ ☐ ☐ ☐ ☐ Helemaal mee oneens
2.	Ik weet/wist niet zeker wat ik moet beslissen Helemaal mee eens ☐ ☐ ☐ ☐ ☐ Helemaal mee oneens
3.	Het is/was duidelijk wat voor mij de beste keuze is Helemaal mee eens ☐ ☐ ☐ ☐ ☐ Helemaal mee oneens
	Factoren die bijdragen aan de onzekerheid
4.	Ik ben/was mij bewust van de keuze die ik moe(s)t maken tussen de verschillende opties Helemaal mee eens ☐ ☐ ☐ ☐ ☐ Helemaal mee oneens
5.	Ik heb/had het gevoel dat ik op de hoogte ben van de voordelen van de innovatieve (nieuwe) preventieve strategie Helemaal mee eens ☐ ☐ ☐ ☐ ☐ Helemaal mee oneens
6.	Ik heb/had het gevoel dat ik op de hoogte ben van de voordelen van beide opties Helemaal mee eens ☐ ☐ ☐ ☐ ☐ Helemaal mee oneens
7.	Ik heb/had het gevoel dat ik op de hoogte ben van de nadelen (risico's en bijwerkingen) van de huidige standaard preventieve strategie Helemaal mee eens ☐ ☐ ☐ ☐ ☐ Helemaal mee oneens
8.	Ik heb/had het gevoel dat ik op de hoogte ben van de nadelen (risico's en bijwerkingen) van de innovatieve (nieuwe) preventieve strategie Helemaal mee eens ☐ ☐ ☐ ☐ ☐ Helemaal mee oneens
9.	Ik heb/had meer advies en informatie nodig Helemaal mee eens ☐ ☐ ☐ ☐ ☐ Helemaal mee oneens
10.	Ik weet hoe belangrijk de voordelen van elke optie zijn/waren bij het nemen van deze beslissing Helemaal mee eens ☐ ☐ ☐ ☐ ☐ Helemaal mee oneens
11.	Ik weet hoe belangrijk de nadelen van elke optie zijn/waren bij het nemen van deze beslissing Helemaal mee eens ☐ ☐ ☐ ☐ ☐Helemaal mee oneens
12.	Het is moeilijk te bepalen of de voordelen belangrijker zijn dan de nadelen of andersom Helemaal mee eens ☐ ☐ ☐ ☐ ☐Helemaal mee oneens
13.	Ik voel(de) me bij het nemen van de beslissing door anderen onder druk gezet Helemaal mee eens ☐ ☐ ☐ ☐ ☐ Helemaal mee oneens
14.	Ik krijg/kreeg voldoende steun van anderen bij het maken van deze beslissing Helemaal mee eens ☐ ☐ ☐ ☐ ☐ Helemaal mee oneens

Beantwoord de volgende vragen alleen als u de beslissing al heeft gemaakt

15.	Ik heb/had het gevoel dat ik goed geïnformeerd was toen ik deze beslissing nam Helemaal mee eens ☐ ☐ ☐ ☐ ☐ Helemaal mee oneens
16.	Deze beslissing geeft aan wat voor mij belangrijk is/was Helemaal mee eens ☐ ☐ ☐ ☐ ☐ Helemaal mee oneens
17.	Ik verwacht dat ik bij mijn beslissing blijf Helemaal mee eens ☐ ☐ ☐ ☐ ☐ Helemaal mee oneens

18.	Ik ben tevreden over mijn beslissing Helemaal mee eens ☐ ☐ ☐ ☐ ☐ Helemaal mee oneens

Decision Regret Scale (DRS).

U bent inmiddels behandeld. De volgende vragen gaan over hoe u achteraf terugkijkt op de keuze die u heeft gemaakt. Geef voor de volgende uitspraken aan in welke mate u het met deze uitspraken eens bent.

	Geheel mee oneens	**oneens**	**Niet oneens, niet eens**	**eens**	**Geheel mee eens**
1. Het was de juiste keuze					
2. Ik heb spijt van de beslissing die is genomen					
3. Ik zou dezelfde keuze maken als ik het zou moeten overdoen					
4. De keuze heeft mij veel schade gedaan					
5. De beslissing was een wijze beslissing					