Title page

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Sentinel lymph node detection in endometrial cancer. A consolidation study.

Appendix to:

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Sentinel lymph node detection in endometrial cancer. A consolidation study.

Table 1. Participating Sites and Site-Principal Investigators

Site	Site-PI	# patients enrolled
1.Department of Obstetrics and Gynecology, Skåne University Hospital and Lund University, Lund, Sweden	Jan Persson MD, PhD	XX
2. To be decided		

Supplementary appendix

Persson J et al

Sentinel lymph node detection in endometrial cancer. A consolidation study.

Coordinating Center: Department of Obstetrics and Gynecology, Skåne, Lund University Hospital and Lund University, Lund Sweden.

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Study Statistician:
Filip Mörk. Faculty of Engineering, Lund University.

Overview study plan.

Consecutive eligible high and low risk endometrial cancer planned for robotic surgery, clinically with the primary tumor confined to the uterus (uterine stage I-II).
High risk defined as at least either of deep (>=50%) myometrial invasion, cervical stromal invasion, endometrioid cancer FIGO grade 3, or a non-endometrioid histology. FIGO grade 1-2 endometrioid cancer with no myometrial invasion are defined as low risk.

Consenting women

Preoperative bilateral measurement of leg volume. Preoperative QOL lymphatic system. (attachment)

Cervical injection of ICG

Registration of adverse events during insufflation and placement of port including necessary adhesiolysis.

Surgery according to the preoperative assignment :

Define/ plan also as of below:

1. □ **FIGO grade 1-2 endometrioid cancers regardless of myometrial invasion.**
SLN UPP and parametria. Ipsilateral reinjection only if non-display of UPP. No frozen section of SLN unless macro. Removal of nodes at typical positions for SLN (External, obturator, common) in case of non-display of UPP uni or bilaterally

2. □ **FIGO grade 3, undifferentiated or non-endometrioid cancers.**
SLN UPP, parametria and LPP. Ipsilateral reinjection if non-display of UPP. Removal of nodes at typical positions for SLN (External, obturator, common) in case of non-display of UPP uni or bilaterally. Full uni-bilateral presacral LND if non-display of LPP. No frozen section of SLN unless macro.

3. □ **Any endometrial cancer with cancer suspect pelvic or paraaortic nodes**
according to RECIST criteria (>=16 mm short axis). SLN detection/reinjection as for 2 above. Frozen section of SLN. Patient upfront surgery planned for pelvic and paraaortic lymphadenectomy. Pelvic and paraaortic LND if frozen section verifies cancer.

UPP- Upper paracervical pathway
LPP- Lower paracervical pathway
Parametria= upper lymphovascular paracervical tissue medial of the umbilical artery, dorsal of the supravesical artery, lateral of the medial broad ligament and ventral of the ureter.

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Pelvic SLN identification with near infrared technique for identification of Indocyanine green (ICG) in lymphatics and lymph nodes. Ipsilateral cervical reinjection of ICG as of above 1-3. Registration of SLN- associated intraoperative adverse events.

Complete pelvic lymphadenectomy and a Querleu-Morrow Type A to C1 hysterectomy and bilateral adnexectomy. Registration of associated intraoperative adverse events.

SLN's for ultrasectioning and immunohistochemistry. Any remaining nodes for standard pathological bisectioning and staining with hematoxylin/Eosine.

Restaging surgery in case of a positive SLN. US and IHC of restaged nodes if compatible with department of pathology.

Registration of postoperative adverse events until 30 days after surgery

At one year postop or at symptoms. Postoperative bilateral measurement of leg volume. Preoperative QOL lymphatic system and symptom score.

Table of contents

1. OBJECTIVES

To estimate the efficacy of a pelvic sentinel lymph node (SLN) concept for diagnose of pelvic nodal metastases in patients with low and- high risk endometrial cancer using a cervical injection of Indocyanine Green (ICG) as tracer and robot assisted near infrared (NIR) imaging using an anatomically based surgical algorithm and definition of sentinel lymph nodes. The observed percentage of metastatic sentinel nodes will be evaluated from a non-inferiority perspective based on an assumed percentage of pelvic nodal metastases estimated from final detailed histological data (myometrial invasion, cervical stromal invasion, histological type and grade)

To estimate the proportion of low- and high risk endometrial cancer patients suitable for the SLN concept in conjunction with robotic surgery

To estimate time for the SLN procedure and intraoperative complications associated with detection of SLN as such (study intervention) and postoperative adverse events until 30 days as well as objective measurement of leg volume and lymphedema symptoms by the use of a validated questionnaire up and until two years after surgery.

To estimate health economy aspects of the SLN concept.

To estimate complications associated with ICG as tracer

2. BACKGROUND

The surgical approach for endometrial cancer staging has changed from conventional laparotomy to a more minimally invasive technique with proven advantages in terms of less perioperative morbidity. In endometrial cancer, nodal involvement is a strong prognostic factor and also determines adjuvant treatment. Therefore information on nodal metastases is important and in many countries a full pelvic and paraaortic lymphadenectomy is recommended despite an increased risk for lymphatic complications in form of lymphedema, lymphocysts and in rare cases lymphatic ascites. The concept of identifying nodal metastases by detection of sentinel lymph nodes as a marker of nodal metastatic disease or not therefore is appealing.

Recent data from the department of Obstetrics and Gynecology in Lund shows that robot assisted surgery with detection of sentinel lymph nodes with the use of ICG is feasible 84% of unselected endometrial cancer patients selected for primary surgery using the inclusion criteria in this study. Recent data also shows a 94% bilateral detection rate of sentinel nodes (technical success rate) and a 98% sensitivity for the SLN-ICG concept for detecting pelvic nodal metastases.

By the use of Indocyanine green, a fluorescent tracer, we have also previously demonstrated two bilateral separate pelvic pathways, the upper paracervical pathway (UPP) running along the upper lymphovascular parametrium usually to external iliac and/ or obturator nodes and the further lateral to the common iliac artery to paraaortic nodes and the lower paracervical pathway (LPP) running via the sacrouterine ligament to nodes medial of the internal iliac artery and/ or presacral nodes then further medial to the common iliac artery to paraaortic nodes. Hence there are two bilateral pelvic pathways draining further to the paraaortic region below as well as above the inferior mesenteric artery. Therefore we believe that lower paraaortic SLN can only be defined in the absence of pelvic SLN along the pathways but with clear filling of pelvic lymphatic channels up to the aorta. In previous studies and pilot studies at our institution we have never observed this situation.

Alternatively, lymph nodes cranial of the inferior mesenteric artery but caudal of the left renal vein (infrarenal, supramesenteric nodes) theoretically may be dyed via the infundibulopelvic ligament and may then be considered as true paraarotic SLN but only in the absence of dyed node more caudally. Neither this situation has been observed after a cervical injection of tracer rarely filling the infundibulopelvic ligament. Moreover, attempts

to find paraaortic SLN would be a step away from decreasing surgery in endometrial cancer. Although detection of pelvic SLN may miss paraaortic skip metastases we hypothesize that ultrasectioning of SLN and including a presacral dissection of SLN may decrease the incidence of true paraaortic skip metastases.

Surgical competence and experience is necessary to achieve a high technical success rate and a low false negative rate for SLN.
This study aims to evaluate the pelvic sentinel node concept based on a defined surgical algorithm and with a clear definition of SLN based on described uterine lymphatic anatomy. The study setting includes only high volume accredited surgeons enabling an evaluation of the true potential of the pelvic SLN concept in endometrial cancer.

This study aims to include consecutive low and high endometrial cancer patients fulfilling criteria to ensure the results are representative for the endometrial cancer population.

3. PATIENT ELIGIBILITY

Inclusion Criteria

-Women of age 18 years and older at the time of informed consent.

-Women with a pathologically proven endometrial carcinoma of any histologic subtype or grade, clinically stage I-II planned for primary surgery

-A uterine size allowing minimally invasive surgery

-Women must be able to understand and sign an informed consent in Swedish language.

-Absence of any exclusion criteria

Exclusion Criteria

-Non consenting patients

-Ongoing pregnancy

-Inability to understand written and/or oral study information

-WHO performance status or conditions contraindicating adjuvant oncological treatment (WHO III or more with no BMI limit)

-Previous lower limb lymphedema (only for the lymphedema part of study)

-Evidence of locally advanced disease or intraabdominal/distant metastases at preoperative CT, MRI or ultrasonography.

-Surgical contraindication to a laparoscopic approach or lymphadenectomy at surgeons discretion.

-Anesthesiologic contraindication to a laparoscopic approach at the anesthetist's discretion

-Allergy to Iodine

-Patients with a known liver disease

-Patients with a bleeding disorder or mandatory antithrombotic treatment.

WHO Performance status

Grade	Explanation of activity
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Surgeon eligibility

All included surgeons outside the primary investigating center must have had a case observation at the primary investigating center followed by a an approved site visit by the principal investigating surgeon at their home center ensuring adherence to protocol. All included surgeons at the primary investigating center were approved by the principal investigating surgeon.

All included surgeons must have a previous experience of at least 100 robot-assisted procedures.

In case of additional centres later including patients: The departments of pathology shall be coordinated in terms of principles for ultra sectioning and immunohistochemistry of SLN and management on non-sentinel lymph nodes.

4.0/5.0 STUDY MODALITIES/ TREATMENT

Surgical Procedures

All patients; plan for QM B2 or C1 hysterectomy stage II), adnexectomy. Omentectomy in non-endometrioid or undifferentiated cancers

Define/ plan also as of below:

1. □ **FIGO grade 1-2 endometrioid cancers regardless of myometrial invasion.**
SLN UPP and parametria. Ipsilateral reinjection only if non-display of UPP. No frozen section of SLN unless macro. Removal of nodes at typical positions for SLN (External, obturator, common) in case of non-display of UPP uni or bilaterally

2. □ **FIGO grade 3, undifferentiated or non-endometrioid cancers.**
SLN UPP, parametria and LPP. Ipsilateral reinjection if non-display of UPP. Removal of nodes at typical positions for SLN (External, obturator, common) in case of non-display of UPP uni or bilaterally. Full uni-bilateral presacral LND if non-display of LPP. No frozen section of SLN unless macro.

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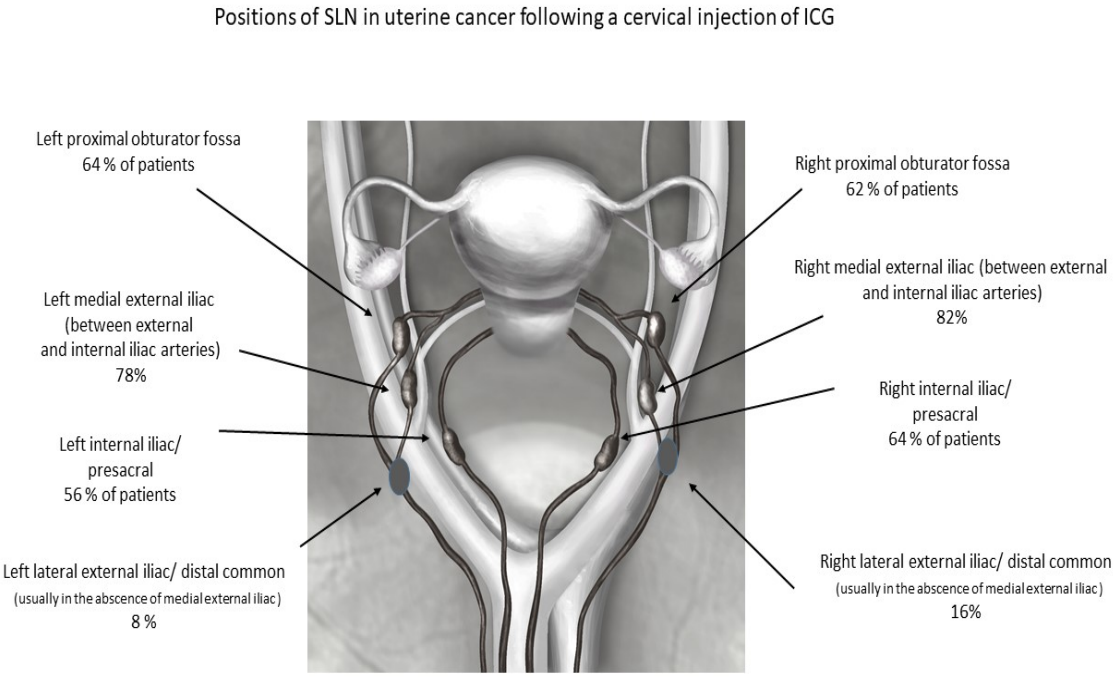
UPP- Upper paracervical pathway
LPP- Lower paracervical pathway
Parametria= upper lymphovascular paracervical tissue medial of the umbilical artery, dorsal of the supravesical artery, lateral of the medial broad ligament and ventral of the ureter.

Typical positions of SLN for definition of "SLN-anatomy"



Drug Information:

Indocyanine Green solution (ICG) 2.5mg/mL.

Description: ICG (Pulsion medical system, PICG0025SE, Feldkirchen Germany) is a sterile, lyophilized green powder containing 25 mg of Indocyanine green with no more than 5% sodium iodide.

The ICG solution is prepared immediately before surgery and intended for single patient use. For preparation, 10mL of sterile water is injected directly into the lyophilized ICG in its glass vial. Invert the vial multiple times to ensure thorough mixing. Draw up 0,25 mL in six 1 mL syringes from the vial with ICG solution (2,5mg/mL) for the cervical injection. A 0.6x38mm 23Gx1 ½ needle. The content of four of the syringes are used for the initial injection and in case of non-display of any pathway one or two of the other are used for an ipsilateral re-injection.

The ICG solution is stored at room temperature. The solution is active for 6 hours, and should be discarded after that period of time.

Manufacturer: Pulsion medical system, Feldkirchen Germany
Availability: ICG will be provided by the manufacturer to each site.

Adverse Effects if ICG: All adverse effects are allergic in nature and occur in <1% of patients. Anaphylactic or urticarial reactions have been reported in patients with or without a history of allergy to iodides. If such reactions occur, treatment with the appropriate agents (e.g. adrenalin, antihistamines, corticosteroids) should be initiated.
Contraindications: Known hypersensitivity to iodine containing compounds. Known liver failure. Radioactive iodine uptake studies should not be performed for at least 1 week following the use of ICG.

Please refer to the current ICG package insert for complete prescribing information

Injection of Indocyanine Green (ICG)

- The ICG is prepared by thorough mixing of 10mL of sterile water with the lyophilized ICG in its vial creating a 2.5mg/mL concentration. The lot number, expiration date and dose injected (mg) will be recorded.
- Six separate sterile 1mL syringes is prepared with 0.25 mL ICG solution (0.625 mg ICG)in each syringe is prepared.
- A 0.6x38 mm 23G needle is attached to each syringe for the injection. A separate back table is used for the syringes.
- The ICG injection will be performed immediately before placement of surgical port and docking the robot.
- Half the ICG volume in each syringe is injected submucosally and half the volume 3 cm into the cervical stroma at 2-4-8-and 10 O'clock respectively to a total dose of 2.5mg ICG and a total volume of 1 mL. Time for injection is recorded.
- After injection of dye, a fornix presenter without an intracervical device is placed
- A second ipsilateral injection of 0,25mL ICG is performed in case of non-display of either of the upper (UPP) or lower (LPP) paracervical pathways after a minimum of 10 minutes observation time after ICG injection. The injection is done at 3 and 9 O'clock respectively, half the volume submucosally and half the volume 3 cm into the cervix.
- Display of the separate lymphatic pathways (UPP, LPP and IPP will be recorded after the first and if performed after the second injection).

Sentinel Node Identification

The bilateral technical success rate of SLN identification is important to determine if this technique can be transferred to clinical practice. A clear anatomically definition of what is a SLN and a strict surgical algorithm as described in this study is important. Based on recent results from our institution on cervical and endometrial cancer we expect that the bilateral pelvic SLN identification (defined as at least one SLN per hemipelvis) will be 94%. A lower than expected detection rate will not be an incentive for premature stop of accrual. Importantly, accreditation of surgeons will be performed as described and is likely important to achieve a similar success rate as in previous studies.

The sentinel nodes are defined as the juxtauterine ICG positive node with an afferent ICG positive lymphatics in each of the UPP and LPP respectively on each pelvic side with the potential of parallel lymphatics in the UPP to the external and obturator areas. These SLN are defined as **SLN type 1.**

In case of a ICG positive lymph vessel where no nodes are ICG positive in that pathway, the node where the ICG positive lymphatic channel ends is defined as **SLN type 2**.

Nodes macroscopically suspect of metastatic disease will be defined as **SLN Macro** regardless of ICG uptake but with information on ICG positivity or not.

In case of no defined SLN 1-2 macro along the UPP and no **SLN macro** (low and high risk EC) nodes at typical positions shall be removed and regarded as **SLN-anatomy** and treated as SLN by the department of pathology. Likewize all endometrial cancers of FIGO grad III, undifferentiated or of non-endometrioid histology shall have a full presacral dissection in case of non-display. Those node shall be treated as SLN by the department of pathology.

Importantly, to secure accuracy, the positions and types of SLN will be marked on an anatomical chart, recorded on a list with anatomical locations and placed in pre-labeled jars with corresponding anatomical positions and numbers. This list is used by the department of pathology for reporting the results to minimize the risk of errors in location of nodes and which nodes are SLN's and non-SLN's. A copy of the list is kept in the patients study file. Nodes defined as SLN will have red labels on the jars, other nodes will have black labels. SLN's will be sent for final histological evaluation including ultrasectioning and immunohistochemistry as described. SLN's will not be sent for frozen section unless clinically motivated.

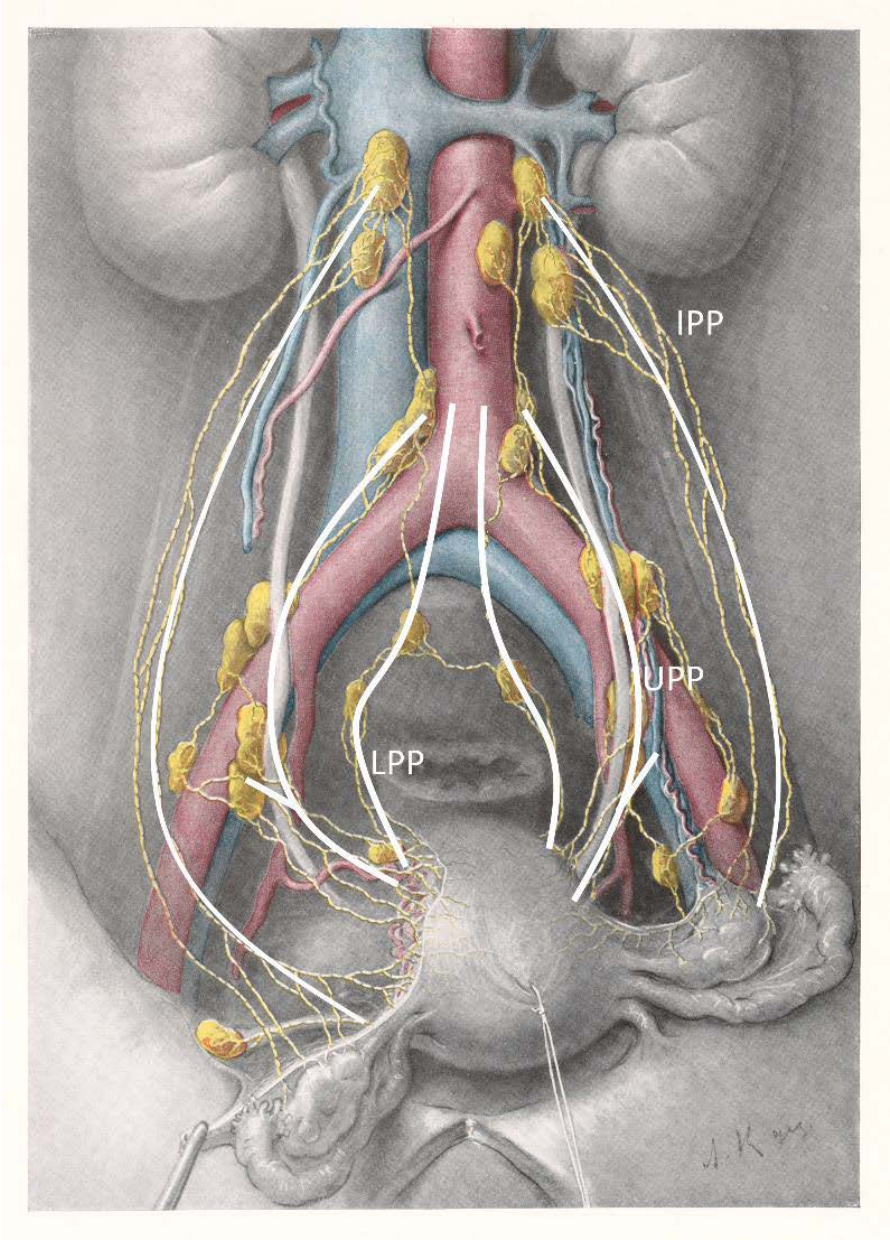
The display of ICG along the UPP shall be evaluated a minimum 10 minutes after the injection of ICG, first transperitoneally, and if not seen, after opening of the retroperitoneal avascular planes. An ipsilateral reinjection shall be performed in case of non-display of the UPP in both low risk (LREC) and high risk (HREC) endometrial cancers. A non-display of the LPP shall ***not*** motivate reinjection but in HREC a full presacral lymphadenectomy (LND). No presacral dissection shall be performed in LREC.

In case if non-display of the UPP despite reinjection a full lymphadenectomy in the external iliac and obturator areas shall be performed in HREC whereas In LREC LND a selective LND shall be performed including all macroscopically enlarged nodes and lymph nodes proximal in the obturator fossa and external iliac nodes in the bifurcation / between the external and internal iliac artery (typical positions of SLN's along the UPP).

To minimize disturbance by leaking ICG identification and removal of SLN's starts cranially, presacrally (along the LPP, HREC only) and continues at the pelvic side walls along the UPP. In both HREC and LREC and after removal of SLN's the upper lymphovascular parametrial tissue is removed separately (defined as the tissue along the uterine artery, medial to the obliterated umbilical artery and caudal of the supravesical artery) as it may contain lymph nodes that may not be separated from the green lymphovascular tissue and hence be the juxtauterine lymph node.

Anatomic boundaries of lymph node compartments in the female pelvis				
Lymph node compartment	Proximal limit	Lateral limit	Distal limit	Medial limit
External iliac area	Bifurcation of external and internal iliac artery	Genitofemoral nerve	Cloquets lymph node	External iliac vein
Obturator fossa	Internal iliac vein	Ileopsoac muscle	Os pubis, obturator nerve	Obliterated umbilical artery
Common iliac	Aortic bifurcation	Genitofemoral nerve	Bifurcation of external and internal iliac artery	Common iliac artery
Presacral	Aortic bifurcation	Common iliac artery	Lower promontory	Hypogastric nerve (as distinction between right and left)

Anatomic description of lymphatic pathways draining the uterus



The upper paracervical pathway (UPP) follows the uterine artery to the pelvic side wall draining primarily to the external iliac and obturator nodal compartments, then running lateral to the common iliac artery further to the paraaortic area.

The lower paracervical pathway (LPP) follows the ventral rim of the sacrouterine ligament, primarily to internal iliac and presacral nodes, then running medial of the common iliac artery further to the paraaortic area.

The infundibulopelvic ligament pathway (IPP) runs via the Ip-ligament further to the supramesenteric paraaortic area.

For the pelvic SLN concept, ideally one SLN should be identified per LPP and UPP per pelvic side wall.

Anatomic plan for localization of sentinel lymph nodes

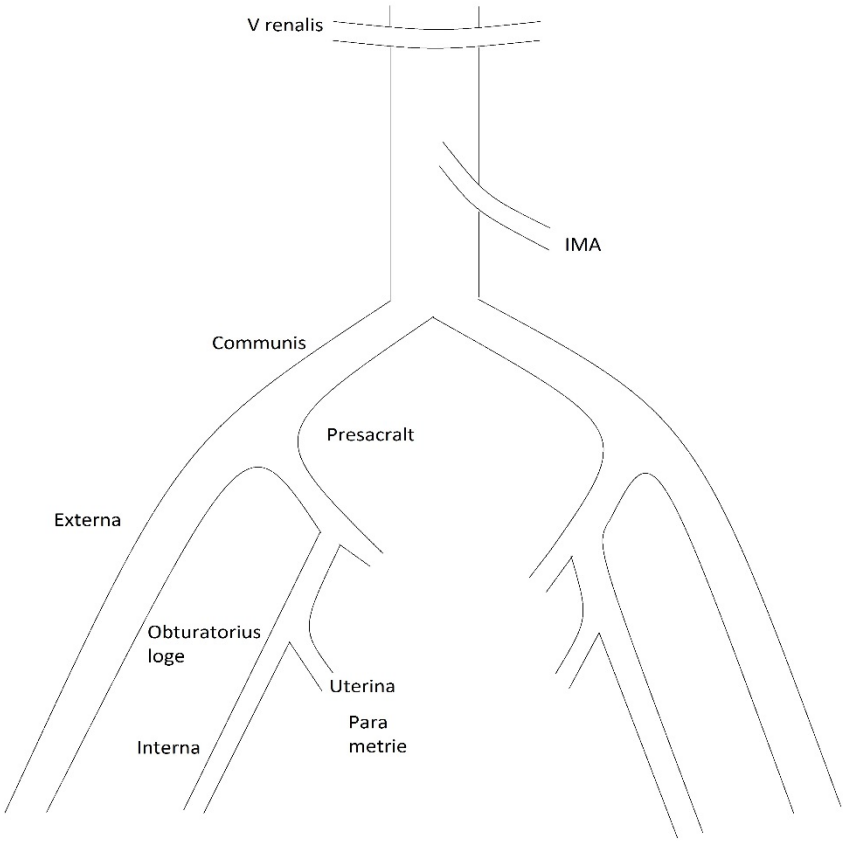
Injection site of ICG ☐ cervix Reinjection cervix: ☐ yes ☐ no

Display after first injection

	UPP	LPP	IP-ligament
Right			
Left			

Display after second injection

	UPP	LPP	IP-ligament
Right			
Left			



Mark position and type of SLN on anatomical chart with number corresponding to position and number at list and on separate jars for each SLN.

O = ICG positive juxtauterine Sentinel node **(SLN1**)

☐= ICG neg juxtauterine lymph node with afferent lympahtic vessel **(SLN 2)**

X = Tumor suspect lymph nodes regardless of mapping **(SLN makro)**

List of nodal specimens (swedish) Endometrial cancer pat-id date

Om preparat saknas från station stryks raden i listan. Burknumrering behålls för övriga prep.

KK Burk nr	Körtelposition	Patol burk nr	Dosa nr	Antal bitar	Mikro Antal körtlar	Varav med metast
1	Uterus, höger ovarium & tuba, vänster ovarium & tuba					
2	Lgl Iliaca Externa höger ICG NEG					
3	Lgl Iliaca Externa höger ICG POS					
4	Lgl Obturatorius höger ICG NEG					
5	Lgl Obturatorius höger ICG POS					
6	Lgl Iliaca Communis höger ICG NEG					
7	Lgl Iliaca Communis höger ICG POS					
8	Lgl Presacralt höger ICG NEG					
9	Lgl Presacralt höger ICG POS					
10	Lgl Iliaca Externa vänster ICG NEG					
11	Lgl Iliaca Externa vänster ICG POS					
12	Lgl Obturatorius vänster ICG NEG					
13	Lgl Obturatorius vänster ICG POS					
14	Lgl Iliaca Communis vänster ICG NEG					
15	Lgl Iliaca Communis vänster ICG POS					
16	Lgl Presacralt vänster ICG NEG					
17	Lgl Presacralt vänster ICG POS					
18	Lgl Paraaortalt nedom IMA ICG NEG					
19	Lgl Paraaortal nedom IMA ICG POS					
20	Lgl Paraaortal ovan IMA ICG NEG					
21	Lgl Paraaortalt ovan IMA ICG POS					
22	SLN Parametrium höger					
23	SLN Parametrium vänster					
24	SLN typ 1 presacralt höger					
25	SLN typ 1 presacralt vänster					
26	SLN typ 1 iliaca externa höger					
27	SLN typ 1 obturatorius höger					
28	SLN typ 1 iliaca externa vänster					
29	SLN typ 1 iliaca obturatorius vänster					
30	SLN typ 1					
31	SLN typ 1					

32	SLN typ 2					
33	SLN typ 2					
34	SLN makro ICG pos ICG neg					
35	SLN makro ICG pos ICG neg					
36	SLN anatom iliaca externa höger					
37	SLN anatom Iliaca externa vänster					
38	SLN anatom obturatorius höger					
39	SLN anatom obturatorius vänster					
40	SLN anatom communis höger					
41	SLN anatom communis vänster					
42	SLN anatom presacralt höger					
42	SLN anatom presacralt vänster					

Numbers 30-35 will be used for describing locations outside the most common sites and for SLN type 2 and SLN macro as appropriate. The locations will be written by hand on list and labels for jars.

Histopathologic evaluation of the sentinel nodes and the non-sentinel nodes.

All macroscopically identified SLN lymphoid tissue will be embedded and bisected if the minimum thickness exceeded 3 mm. If no macroscopically lymphoid tissue is identified in SLN or parametrial tissue the most suspicious find will be embedded and microscopically investigated. Ultrastaging using hematoxylin/ Eosin staining will be performed in five sections at three different levels, separated by 200 µm, if the maximum diameter of the SLN tissue exceeds one mm. From first and second level immunohistochemistry (pan-cytokeratin, MNF 116) will be performed. If no macroscopically lymphoid tissue is identified in SLN or parametrial tissue the most suspicious find will be embedded and microscopically investigated. ITC can be detected by Hematoxylin/Eosin or by Immunohistochemistry alone.

Non-SLN will be bisected. Non-SLN less than 3 mm in thickness will be embedded whole, and from nodes thicker than 3 mm at least half the node will be embedded. The slides will be evaluated after hematoxylin/Eosin staining.

Classification of tumor size in SLN's

Sentinel nodes will be classified according to a modification of the AJCC staging for axillary nodes from breast cancer as follows:

Macrometastases = tumor greater than 2.0 mm in diameter.

Micrometastases = tumor cell aggregates between 0.2 and 2.0 mm in diameter.

Isolated tumor cells =individual tumor cells or aggregates that are less than 0.2mm in diameter, usually detected by immunohistochemistry.

Tumor absent – no tumor cells identified in H&E (or immunohistochemically, if applicable) stained sections.

Non-sentinel lymph nodes will be reported as positive or negative for metastases based upon routine sectioning and examination of a single H&E stained section.

5.0 TREATMENT PLAN/ FOLLOW UP

Patients with metastatic SLN's shall be planned for a restaging procedure including pelvic and paraaortic lymph nodes.

Importantly, all intraoperative adverse events associated with the study intervention and the study drug (ICG) will be recorded in protocol as the separate time used for the detection and removal on SLN's. Likewize, complications associated with the restaging procedure shall be included on an intention to treat basis.(additional CRF)

All adverse events, including postoperative until 30 days, hall be evaluated whether attributable to the study intervention or not.

Measurement of leg volume as an objective parameter of lymphedema shall be performed at one and two year follow up and at symptoms.

Symptoms associated with lymphedema shall be evaluated by a designated QoL Form used before surgery, after surgery at symptoms, and at one and two years after surgery. A symptoms score shall be used at every follow up.

NOTE: Surgeons' skill and adherence to protocol will be verified as described above.

6.0 TREATMENT MODIFICATIONS

In case of conversion to open surgery before identification and removal of SLN's the patients should be included in evaluation of adverse events and feasibility on an intention to treat basis but not included in the calculation of sensitivity and negative predictive values for the sentinel node concept.

A pelvic lymphadenectomy shall be performed based on definition of "SLNmacro" and/or "SLN-anatomy". SLN macro shall be evaluated with frozen section and if positive a paraaortic lymphadenectomy shall be performed unless contraindicated.

7.0 STUDY CRITERIA

Observations and Tests

The following observations and tests are to be performed and, where appropriate, recorded on the designated form(s) (Appendix A):

PARAMETER	Pre-operative	Intraoperative	Postoperative
Log on approached patient	X		
Log on included patients and patients' withdrawal from study before surgery	X		
History & Physical examination Examination and evaluation by surgeon and anesthetist	X		
Measurement of leg volume	X		X
Lymphedema Quality of Life questionnaire	X		X
Lymphedema symptoms score			X

Laboratory test Hb, S-electrolytes, S-kreatinine CRP, Trc, coagulation test when appropriate	X		X
Injection data for ICG including drug related adverse events	X	X	X
Sentinel nodes identification		X	
Recording of intraoperative adverse events		X	
Histologic evaluation of sentinel nodes and non-sentinel nodes			X
Recording of post-op complications until 30 days after surgery (Claviden Dindo)			X

Adverse Events will be captured from time of ICG administration until 30 days aftger surgery. See section 10.

8.0 EVALUATION CRITERIA

- All patients who are injected with ICG with at least one SLN type1-2, macro and SLN anatomy and not converted to open surgery before detection and removal of SLN's will be included for evaluation of detection rate of metastatic pelvic nodes all together and with evaluation of ICG defined (SLN type1-2) separately.

- Time used for the study intervention (Injection and reinjection of ICG and detection / removal of SLN's) shall be separately recorded

- All patients included, regardless of conversion to open surgery and mapping of ICG will be included in the overall evaluation of feasibility and safety.

- Intraoperative adverse associated with the detection and removal of SLN will be evaluated and reported separately on all patients who have at least one SLN removed regardless of type, i.e all patients in whom SLN were removed separately.

- Postoperative complications until 30 days after surgery will be reported.

-Perioperative and postoperative complications related restaging will be evaluated on an intention to treat basis.

-An increase in leg volume of 10 % or more compared with the preoperative volume will be defined as a new onset of lymphedema.

9.0 DURATION OF STUDY

The study includes hysterectomy with identification of sentinel lymph nodes on consecutive LREC and HREC patients.
The patient may withdraw from the protocol at any time prior to surgery or at any time until retrieval of postoperative data until 2 year after surgery.

The study was initiated at Lund university hospital (From january 2019) with potential later inclusion of a second or mores investigating centers which will motivate a revision of the study protocol related estimated time for enrollment of patients and for accreditation of the second centre and surgeons. The annual volume of endometrial cancer patients in Lund is close to 200 with an estimated 85% suitable for minimally invasive surgery and inclusion in the study.
Related statistical analyses below a total of 362 patients will need to be included with an interim analysis after 150 patients.

10 STUDY MONITORING AND REPORTING PROCEDURES

ADVERSE EVENT REPORTING

The study protocol has been revised related principles study monitoring and for reporting adverse events to the principal investigating center after inclusion of the second center.

Definitions

An adverse event (AE) is any new medical problem or exacerbation of an existing problem experienced by a subject enrolled in the study, whether or not it is considered drug-related by the investigator.

This study will utilize the Adverse Events Logs (Tables 10.1-5). Any SAE will be reported to the study coordinator (Michele.bollino@med.lu.se) using the SAE log. (appendix 1).

Adverse events related to the study drug (ICG).
All adverse events occurring from the first dose of study drug until hospital discharge (whether or not attributed to the study drug) will be reported on the Adverse Event Log. In addition, any adverse event reported by the subject to the investigator after discharge and determined to be reasonably associated with the study drug should also be captured and followed until resolution.

Adverse events related to the sentinel node procedure as such (excluding AE related the study drug, ICG)
All intraoperative events related to the SLN procedure will be reported on the adverse events log.

Adverse events related the surgical procedure (excluding the SLN part) including AE until 30 postoperative days.
All adverse events will be reported on the adverse events log.

Serious adverse event (SAE):

An adverse event that results in one or more of the following:

-Any death occurring prior to the postoperative outpatient evaluation 30 days postoperatively.

-Any life-threatening event until and including 30 postoperative days.

-Any medical event requiring inpatient hospitalization or prolongation of existing hospitalization beyond five postoperative days

NOTE: Hospitalizations that are not considered SAE are:

-Hospitalization planned prior to first administration of study drug

-Hospitalization for elective treatment of a pre-existing condition unrelated to the study medication

- Hospitalization due to social / practical reasons such as an untimely coordination with local community home care services.

Attribution: Attribution is the determination of whether an adverse event is related to a medical treatment or procedure. The categories of attribution are:

Definite: The adverse event is clearly related to the study drug

Probable: The adverse event is likely related to the study drug.

Possible: The adverse event may be related to the study drug.

Unlikely: The adverse event is doubtfully related to the study drug.

Unrelated: The adverse event is clearly NOT related to the study drug.

Unexpected Adverse Event: An unexpected adverse event is an event not mentioned in the package insert/ manufacturer's instructions or the specificity or severity of which is not consistent with the package insert/ manufacturer's instructions.

The grading described beneath and the attribution described above will be used for cathegorization of unexpected adverse events.

Participating Center Reporting Responsibilities

Reporting to the study coordinator

Any SAE's must be reported to study Coordinator at Lund University Hospital within 3 working days of discovery of the incident, using the study-specific SAE Form.
Email: Michele.bollino@med.lu.se

The lead and local principal investigators and the study coordinator shall conduct continuous review of data and patient safety for a monthly summary of the included number of patients, patient safety and significant AE's described in the protocol.

All SAE's potentially associated with the study drug, the sentinel node procedure as such or deaths shall be evaluated by a

Reporting to the IRB:

Each participating center will report adverse events to their IRB per local guidelines.

Coordinating Center Reporting Responsibilities

Reporting to the study coordinator, Lund University Hospital
Same criteria as above.

Reporting to the IRB:

Same criteria as above.

The Study Coordinator will distribute reports which are serious, unexpected and associated with the study intervention (possibly, probably or definitely) to all participating investigators. Copies of all serious adverse event reports will be kept on file the department of Obstetrics and Gynecology, Lund University Hospital.

The study coordinator will also report all individual SAE's related to study drug, the sentinel node procedure as such, are life threatening or resulting in death (defined above and in table 10.6) to the Safety Monitoring Committee (SMC) for clinical studies at Skåne University Hospital for an independent evaluation.

At any time during the conduct of the trial, if it is the opinion of the investigators that the risks (or benefits) to the patient warrant early closure of the study, this recommendation should be made in writing to the SMC. Alternatively, the SMC may initiate suspension or early closure of the study based on its review of the investigator reports.

Study Monitoring / study accrual oversight

The study principal investigator, any local principal investigator and study coordinator will conduct meetings (teleconferenced) every 6 months to discuss the protocol. The Study-PI and local-PI can call a meeting to convene at additional times if deemed necessary, for example following statistical review at the interim period if stopping the study for either achieved goals or futility. Apart from the monitoring described below, the number of node positive patients and potential false negative SLN's will be monitored continuously by e-mail to the study coordinator by the use of the study number assigned to each patient.

In case of identified inconsistencies or missing data, additional source documents (identified only by unique patient number) will be requested from the site to resolve ongoing inconsistencies.

The principal investigator and/or the study coordinator will, if deemed necessary by the principal or second participating center perform audits of informed consents and subject eligibility.

Data Management

Preoperative, intraoperative and postoperative data from each surgery will be recorded on the standardized study sheets. These study sheets will be made available to each study site. Each study site will be allocated a study number which will serve as the prefix to the case number. For example, Lund university Hospital will be allocated the prefix "Lu" and the first study patient will have the study number "LU-001. Each investigating center will hold a record with the full identification of patients whereas data otherwise should only identify the patient by the study number (see above).

Staff at the individual centers will be responsible for completing the data collection sheet for each patient and all data will continuously be entered into a common secured password

secured database using the designated study numbers. Upon interim analysis the full data will be monitored by the study coordinator, the principal investigator, local principal investigator and study statistician.

Separate analysis of patient data from individual sites can only be performed with the written permission of the study principal investigator.

Early Study Closure

Death will be reported according to section 10.1 above and per local IRB reporting guidelines. The SMC will review all reported deaths monthly. Early closure of the study will be based on judgement of the SMC.

The study will be stopped for futility reasons as described under the statistics section.

10.1.8. Protocol Deviations

Major protocol deviations shall be reported by mail to the study coordinator. Michele.bollino@med.lul.se and filed at Lund University Hospital using the designated study number. Major protocol deviations include, but are not limited to, violations to inclusion/ exclusion criteria, erroneous preparation of ICG or surgery by a non-accredited surgeon.

Table 10.1. Adverse Events before docking the robot (during injection of ICG, insufflation, port placement and adhesiolysis) including conversions to open surgery for any reason.

STUDY NUMBER	AE/SAE	DESCRIPTION	Grade	Attribution
Example LU001	AE	Converted adhesions	1	No
Example LU002	AE	Allergic reaction on ICG	3	Yes

Table 10. 2. Adverse Events during sentinel node dissection

STUDY NUMBER	AE/SAE	DESCRIPTION	Grade	Attribution
LU001 examples	AE	Bleeding requiring suture	2	Yes
LU002	AE	Obturator nerve damage	3	Yes

Table 10.3. Adverse events during pelvic/ pelvic + paraaortic lymphadenectomy

STUDY NUMBER	AE/SAE	DESCRIPTION	Grade	Attributio
LU001 examples	AE	Bleeding requiring suture or	2	No

Table 10.4. Adverse events during hysterectomy / omentectomy.

STUDY NUMBER	AE/SAE	DESCRIPTION	Grade	Attributi
LU001	AE	Ureteral damage	3	No
LU002	AE	Bowel damage	3	No

Table 10.5. Postoperative adverse events until 30 postoperative days (all events, also potentially unrelated). Clavien Dindo classification

STUDY NUMBER	AE/SAE	DESCRIPTION	Grade	Attributi
LU001	AE	Port hernia	IIIb	No
LU002	AE	Fever of unknown origin	II	No

Table 10.6 Intraoperative Adverse events will be graded according to the following scale:

Grade	Description
Grade 1	Mild; asymptomatic; not interfering with function.
Grade 2	Moderate; symptomatic; interfering with function but not ADL; medical intervention indicated.
Grade 3	Severe; symptomatic; interfering with ADL; operative intervention indicated; IV intervention indicated
Grade 4	Life-threatening; major urgent intervention indicated; disabling.
Grade 5	Death

Postoperative adverse events will be graded according to the Clavien Dindo classification

Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusionsand total parenteral nutritionare also included.
Grade III	Requiring surgical, endoscopic or radiological intervention
- IIIa	Intervention not under general anesthesia
- IIIb	Intervention under general anesthesia
Grade IV	Life-threatening complication (including CNS complications)* requiring IC/ICU-management
- IVa	single organ dysfunction (including dialysis)
- IVb	multiorgandysfunction
Grade V	Death of a patient

11. STATISTICAL CONSIDERATIONS

This study is designed to evaluate the ability of the sentinel node (SLN) technique to determine pelvic lymph node metastases in patients with low- and high risk endometrial cancer as a replacement for a full lymphadenectomy in the latter and as an increased diagnostic procedure in the former.

The main statistical endpoint will be to evaluate the SLN concept by a non-inferiority analysis, i.e its ability to detect nodal metastastic disesase compared with an estimated proportion which with a 50/50% distribution of LREC and HREC result in approximately 12% of women having pelvic nodal metastases. This will be tested against 8% metastastic SLN's as null-hypothesis. With a one-sided analysis (Alfa-error of 5% and 80% power) 362 patients need to be included with a planned interim analysis after 150 patients.

If then 22 or more patients are identified as SLN-node positive the hull-hypothesis will be rejected and the study closed. If 12 or fewer patients are identified as SLN node positive the study will be closed for futility. If the number of node positive patients is between 12 and 21 the study will continue to enroll a total of 362 patients (Fleming, 1982).

The measurements of leg volume/lymphedema are based on an estimated risk for lymphedema following SLN only of 1% (null hypothesis) compared with the group of SLN positive (HREC and LREC) with an estimated risk of 4% (20% node positive with 20 risk of lymphedema) with an estimated distribution between group of 88% SLN negative and 12% SLN positive with restaging (SLN+LND). A total of 169 patients need to be included with a planned interim analysis after 65 patients. If 3 or more patients in the SLN+LND group have lymphedema the null hypothesis can be rejected provided no more than one patient in the SLN only group have developed lymphedema.

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Appendices

Sentinel lymph node detection in endometrial cancer. A consolidation study.

Serious adverse events log. Mail to Michele.bollino@med.lu.se

Per definitions of SAE and attributions as outlined in protocol

Patients study number **Date for SAE**		
Type of SAE	**Yes /no**	**Attribution**
Death		
Life Threatening		
Drug /ICG related		
Intraoperative related the SLN procedure as such		
Intraoperative related the full LND/ hysterectomy		
Postoperative		
Unexpected AE		

Description / outcome of the SAE

Serious adverse event (SAE):

An adverse event that results in one or more of the following:

-Any death occurring prior to the postoperative outpatient evaluation 30 days postoperatively.

-Any life-threatening event until and including 30 postoperative days.

-Any medical event requiring inpatient hospitalization or prolongation of existing hospitalization beyond five postoperative days

NOTE: Hospitalizations that are not considered SAE are:
-Hospitalization planned prior to first administration of study drug
-Hospitalization for elective treatment of a pre-existing condition unrelated to the study medication
- Hospitalization due to social / practical reasons such as an untimely coordination with local community home care services.

Attribution: Attribution is the determination of whether an adverse event is related to a medical treatment or procedure. The categories of attribution are:

Definite: The adverse event is clearly related to the study drug
Probable: The adverse event is likely related to the study drug.
Possible: The adverse event may be related to the study drug.
Unlikely: The adverse event is doubtfully related to the study drug.
Unrelated: The adverse event is clearly NOT related to the study drug.

Unexpected Adverse Event: An unexpected adverse event is an event not mentioned in the package insert/ manufacturer's instructions or the specificity or severity of which is not consistent with the package insert/ manufacturer's instructions.
The grading described beneath and the attribution described above will be used for cathegorization of unexpected adverse events.

Appendix 1. Basic data

Sentinel node EC consolidation study

Studie Sentinel node med ICG vid Endometriecancer
Patientuppgifter
Sida 1/2

Date:……. Personal identification number:…….

CRF number (by study coordinator)

Endometrial cancer:

Histological type/ FIGO grade: ……. DNA-analyes: diploid / non-diploid

Tumor size US/MR Length_____ Anteriopost _____width_____mm

Myometrial invasion >50% enligt MR / ultraljud:	☐ yes	☐ no
Uterine serosal involvement/ locally advanced tumor	☐ yes	☐ no
Cervical stromal invasion MR /US/preop hist:	☐ yes	☐ no
Enlarged pelvic nodes / RECIST >=16mm short axis	☐ yes*	☐ no
Enlarged paraarotic nodes / RECIST>=16mm short axis	☐ yes*	☐ no
Locally advanced cancer/distant metastases	☐ yes**	☐ no

Comorbidity: Overall WHO performance grade:

☐	None	☐	Hypertension	☐	Heart disease
☐	Diabetes mellitus	☐	COL	☐	Thromboembolic
☐	Ongoing anticoag treatm	☐	Neurologic disorder	☐	Other specify

Studie Sentinel node med ICG vid Endometriecancer
Patientuppgifter
Sida 2/2

Previous intrabdominal surgery

☐ no

☐ Upper/ lower midline incision …….

☐ Pfannenstiel incision…….

☐ Laparoskopy/ robot:…….

☐ Other, specify…….

Parity / vaginal deliveries …….

Heredity cancer: no/ yes: specify……

Length meter …… Weight ……

* Plan for frozen section of SLN and SLN macro and full staging. See inclusion criteria file.

**Exclude from study

WHO Performance status

Grade	Explanation of activity
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

_____

Consolidation study Sentinel node in endometrial cancer CRF number (by study coordinator)

Appendix 2 Surgical protocol

Date
Surgeon……Assisting surgeon……..
OR nurse……..Circulating nurse…….

Included as/ planned surgery

☐ Low risk endometrial cancer. SLN only

☐ High risk endometrial cancer, SLN only

☐ High/ low risk endometrial cancer SLN+ pelvic+ paraaortic LND due to preop/ intraop suspect nodes

Reason for an intraoperative deviation from a planned surgery
_____

Previous surgery

1 ☐ No
2 ☐ App
3 ☐ Pfannenstiel
4 ☐ Midline upper
5 ☐ Midline lower
6 ☐ Laparoscopy/ robot
7 ☐ other, specify

Vikt (kg)
Längd (m)

Surgery **(specify all)**

1 ☐ Radical hysterectomy+adnex , QM type
2 ☐ Enkel hysterektomi+ adnex
3 ☐ Sentinel node UPP +LPP
4 ☐ Sentinel node UPP only
5 ☐ Full pelvic LND
6 ☐ Paraaortic LND to LRV
7 ☐ Paraaortic LND to IMA
8 ☐ Omentectomy
☐ Other specify

Pat in OR	time.
First Dr's procedure	time
Time for SLN Onset dissection incl reinj	Minutes:
Last stich	time
Pat out OR	time

Uterus weight (g)

Insufflation technique
☐ Palmer point direct entry
☐ Hasson
☐ Verress needle

Adhesiolysis before onset of surgery
☐no
☐Yes
Total Time for adhesiolysis (before and after docking) (minutes)…….

Nr robot instuments
☐2
☐3
☐4
☐5
☐6

Assistant trocar

☐1	☐ 12mm ☐ disp ☐ non-disp
☐2	☐ 15 mm ☐ disp☐ non-disp
☐3	☐ 18 mm ☐ disp ☐ non-disp
☐4	☐ 5 mm ☐ disp ☐ non-disp

Additonal instruments
☐ Endobag,nr_____
☐ Tachyseal,/ floseal, nr_____
☐ Other specify_____

Bleeding
ml_____

Transfusion
☐ No
☐ Yes nr units:_____

´

Conversion
☐no
☐Yes to laparotomy

Cause of conversion

☐ Robot, technical problem,; specify:_____

☐ Surgery, specify:_____

☐ Anesthesiologically cause; specify:_____

Complications during insufflation or adhesiolysis

☐ None

☐ **Yes. Specify:_____**

Complications during SLN removal

☐ No

☐ **Yes. Specify**:_____

Complications during remaining pelvic LND

☐ No ☐ Not performed

☐ **Yes. Specify**:_____

Complications during remaining paraaortic LND

☐ No ☐ Not performed

☐ **Yes. Specify**:_____

Complications during hysterectomy

☐ No ☐ Not performed

☐ **Yes. Specify**:_____

Technique for removal of uterus

☐ vaginally without bag ☐ vaginally with Endobag

☐ Though abdominal wall in bag, specify why and where.

_____

Technique for removal of nodes

☐ Trough assistant port in bag/container
☐ vaginally in bag

Nodal tissue divided in abdomen to an

☐ No ☐ yes specify

enable removal through port?

Closure of fascia

☐ Assistant port

☐ Optics port (SI robot)

☐ Other ports, specify;_____

Appendix 3. Postoperative symptoms score

Diagnos			
Månader postop			
Avliden Om ja, antal månader efter Operation=	Nej Ja,, ”dead in disease” Ja, “ dead by treatment” Ja, död av orelaterad orsak		
Postoperativa Komplikationer efter hemgång	Nej Ja. Återinläggning pga: Ja. Re-operation pga: Ja. Hematom vaginaltopp Ja, hematom bukvägg Ja, infektion vaginaltopp Ja, urinvägsinfektion Ja, oklar feber Ja, ileus Ja, bråck Ja, trombos / emboli Ja, annat:	Inom 30 dagar	> 30 dagar
Recidiv	Nej Suspekt/ under utredning Ja		
Recidiv-diagnos månader postop			
Diagnossätt **Diagnos av vem** (fritext)			
Lokalisation av recidiv (fritext)			
Pågående recidivbehandling **Vad ?** (fritext)			
Komplikationer			
Komplikationer vid			

uppföljning		
Vaginaltopp	välläkt defektläk Ruptur, mån postop= Vault prolaps mån postop= Kort vagina	
Vaginalt ultraljud	Fri vätska i buken? Om ja, diameter största pöl: Lymfcysta: unilateralt / bilateralt (höger / vänster) Storlek (mm): Symtom: nej/ja : ange vilka	
Lymfkörtlar supraklavikulär	Ua / ej ua	
Lymfkörtlar axillärt	Ua / ej ua	
Lymfkörtlar inguinalt	Ua / ej ua	

Bukvägg Fritext (naturalförlopp, ev reop mm	Ingen Port-hernia, ange vilken port= Portmetastas, ange vilken port= Ruptur rectusmuskel, ange vid vilken port= Info=
Blåstömningsproblem	Nej Ja, ej RIK krävande Ja, RIK krävande
UVI senaste 6 mån	Inga Cystit, ange antal Pyelonefrit: ange antal
Andra komplikationer	Obehag, problem med defekation, smärta…?

Distala lymfödem	**Nej** **Ja**	
Debut när? (mån postop)		
Lokalisering **Gradering enligt CTC 3.0** Def se längst bak i pärmen Om ej ena sidan; ange = 0	Höger =	Vänster =
Kvarstående vid dagens uppföljning ?	Nej Ja; oförändrade Ja; förbättrade Ja; försämrade	Nej Ja; oförändrade Ja; förbättrade Ja; försämrade
Behandling	Nej Ja, kompr underben Ja, kompr helben Ja, kompr+ lymfoterapi	Nej Ja, kompr underben Ja, kompr helben Ja, kompr+ lymfoterapi
Kompressionsstrumpor, klass		
Pittingödem	Nej Ja	Nej Ja
Info/ fritext		
Proximala lymfödem	**Nej** **Ja**	
Debut när: (mån postop)		
Lokalisering	Höger=	Vänster=
Kvarstående vid dagens uppföljning ?	Nej Ja; oförändrade Ja; förbättrade	Nej Ja; oförändrade Ja; förbättrade

	Ja; försämrade	Ja; försämrade
Info / fritext		
Nervpåverkan	Höger	Vänster
n. genitofemoralis **Om ingen; ange= 0**		
n. obturatorius **Om ingen; ange= 0**		
n cut fem lat **Om ingen; ange= 0**		
Rosfeber	Nej Ja, antal gånger=	Nej Ja, antal gånger=
Antibiotika profylax	Ja	Nej

Appendix 4. Lymphedema QoL life questionnaire

Centers initialer ☐ Patients kodnummer ☐

Preoperativt ☐ Vid symptom (= v postop) . ☐ 1 år postop. ☐ 2 år postop. ☐ Datum för ifyllande: _____

Frågeformulär angående lymfödem av ben och livskvalitet (LYMQOL)

Instruktion:
I frågeformuläret finns 30 frågor. Vi ber Dig besvara frågorna genom att sätta en ring runt den siffra som Du anser passar bäst in på Dig. Med ben menar vi lår, knä och underben men inte fot.

	Inte alls	Lite	En hel del	Mycket
Om Du vill ändra Ditt svar sätter Du en kryss över ringen:	1	2	3	⊗
och fyller sedan i rätta svaret:	1	(2)	3	4

Fråga nr	Fråga	Inte alls	Lite	En hel del	Mycket
A	Upplever Du att höger ben är svullet?	1	2	3	4
B	Upplever Du att vänster ben är svullet	1	2	3	4
Om Du har svarat Inte alls i båda fråga A och B var god gå till Fråga 16. Om Du svarat ja i endera var god fortsätt med fråga nr 1 och vidare					
1	Har Ditt / Dina svullna ben påverkat:				
1a	- Din gångförmåga?	1	2	3	4
1b	- Din förmåga att böja Dig för att t.ex. knyta skoband eller klippa tånaglar?	1	2	3	4
1c	- Din förmåga att stå?	1	2	3	4
1d	- Din förmåga att resa Dig ur en stol?	1	2	3	4
1e	- Din förmåga att sköta Ditt arbete?	1	2	3	4
1f	- Din förmåga att utföra hushållsarbete?	1	2	3	4
2	Påverkar bensvullnaden Dina fritidsaktiviteter/Ditt sociala liv?	1	2	3	4
2a	Om ja, var god ge exempel på detta: _____				

 ©Kjölhede 2014 **VAR GOD VÄND OCH FORTSÄTT MED FRÅGORNA PÅ BAKSIDAN**

Fråga nr	Fråga	Inte alls	Lite	En hel del	Mycket
3	I vilken utsträckning är Du beroende av andra människor?	1	2	3	4
4	I vilken utsträckning känner Du att svullnaden påverkar Ditt utseende?	1	2	3	4
5	I vilken utsträckning har Du svårigheter att hitta kläder som passar?	1	2	3	4
6	I vilken utsträckning har Du svårigheter att hitta kläder som Du tycker om att ha på Dig?	1	2	3	4
7	Har Du svårt att hitta sko som passar?	1	2	3	4
8	Har Du svårt att hitta sockar, strumpor eller strumpbyxor som passar?	1	2	3	4
9	Påverkar bensvullnaden Din självkänsla?	1	2	3	4
10	Påverkar bensvullnaden Ditt förhållande till andra människor?	1	2	3	4
11	Orsakar bensvullnaden smärta?	1	2	3	4
12	Har Du domningar i Ditt / Dina svullna ben?	1	2	3	4
13	Har Du stickningar eller pirrningar i Ditt / Dina svullna ben?	1	2	3	4
14	Upplever Du svaghet i Ditt / Dina svullna ben?	1	2	3	4
15	Upplever Du tyngdkänsla i Ditt / Dina svullna ben?	1	2	3	4
Vid svar på de nästa 7 frågorna ska Du tänka hur det har varit <u>under senaste veckan</u>					
16	Har Du haft svårt att sova?	1	2	3	4
17	Har Du haft svårt att koncentrera Dig, t.ex. på att läsa?	1	2	3	4
18	Har Du känt Dig spänd?	1	2	3	4
19	Har Du känt Dig orolig?	1	2	3	4
20	Har Du känt Dig lättretlig?	1	2	3	4
21	Har Du känt Dig nedstämd?	1	2	3	4
22	Sammantaget, hur skattar Du Din livskvalitet för närvarande? Var god markera med ring på nedanstående skalan. (0 = dålig och 10 = utmärkt).				
	0 1 2 3 4 5 6 7 8 9 10				
	<u>Dålig</u>				*<u>Utmärkt</u>*

LYMQOL Swedish version

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