The RACC trial –Robot-assisted Approach to Cervical Cancer

A multi-centre open-label randomised non-inferiority trial of robot-assisted laparoscopic surgery versus laparotomy in women with early-stage cervical cancer

Protocol identification number: RACC Version 1.7

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SYNOPSIS

Protocol Title	**RACC- Robot assisted Approach to Cervical Cancer**
Indication	Participants have operable early-stage cervical cancer.
Primary objective	To investigate the oncologic safety of robot-assisted laparoscopic surgery as compared to standard laparotomy.
Secondary objectives	To evaluate intra and postoperative outcomes, overall survival, diagnostic accuracy of sentinel lymph node biopsy, patient reported quality of life including lymphedema and health care costs.
Study Design	Randomised controlled non-inferiority trial
Planned sample size	1092 women
Inclusion criteria	• Histologically confirmed primary adenocarcinoma, squamous cell carcinoma or adeno-squamous carcinoma of the uterine cervix; • Women with histologically confirmed FIGO stage IB (IB3 excluded) and IIA1 disease • Women undergoing either a Type B or C radical hysterectomy according to Querleu Morrow classification • ECOG Performance Status of 0, 1 or 2 • Patient must be suitable candidates for surgery. • Patients who have signed an approved Informed Consent • Age> 18 years
Exclusion criteria	• Any histology other than adenocarcinoma, squamous cell carcinoma or adeno-squamous carcinoma of the uterine cervix • Tumor size greater than 4 cm • FIGO stage II-IV (except IIA1) • Women with a history of pelvic or abdominal radiotherapy • Women who are pregnant • Women with contraindications to surgery • Women with evidence of metastatic disease by conventional imaging studies, enlarged pelvic or aortic lymph nodes > 2cm; or histologically positive lymph nodes • Serious concomitant systemic disorders incompatible with surgery or study (at the discretion of the investigator) • Women unable to withstand prolonged lithotomy and steep Trendelenburg position • Women with secondary invasive neoplasm in the last 5 years (except non-melanoma skin cancer, breast cancer T1 N0 M0 grade 1 or 2 without any signs of recurrence or activity) • Women with iodine allergy cannot participate in the sentinel node part of the trial (not an exclusion criteria for the primary outcome)

Primary outcome	Recurrence free survival
Secondary outcomes	• Overall survival • Health related quality of life including lymphoedema, bladder and sexual dysfunction • Intraoperative complications • Postoperative complications • Diagnostic accuracy of the pelvic sentinel lymph node concept • Health care costs
Standard treatment	Radical hysterectomy and pelvic lymphadenectomy by laparotomy
Experimental treatment	Robot-assisted laparoscopic radical hysterectomy and pelvic lymphadenectomy
Duration of study including follow up	8-9 years (inclusion 7-8 years and follow-up 1-2 years)

LIST OF ABBREVIATIONS

CC	Cervical cancer
HPV	Human papilloma virus
FIGO	International Federation of Gynecology and Obstetrics
LVSI	Lympho-vascular space invasion
OS	Overall survival
DFS	Disease free survival
EBRT	External beam radiation therapy
ESGO	European Society of Gynaecological Oncology
TMMR	Total Mesometrial Resection
LS	Laparoscopy
TLRH	Total laparoscopic radical hysterectomy
PLND	Pelvic lymph node dissection/lymphadenectomy
PALND	Paraaortic lymph node dissection/lymphadenectomy
US FDA	United States Food and Drug Administration
RALS	Robot-assisted laparoscopic surgery
OT	Operation time
LT	Laparotomy
US	United States
NCDB	National Cancer Database
MIS	Minimally invasive surgery
SGO	Society of Gynecologic Oncologists
LACC	Laparoscopic Approach to Cervical Cancer
HR	Hazard Ratio
CO_2	Carbon dioxide
SQRGC	Swedish Quality Registry for Gynecologic Cancer
SNB	Sentinel node biopsy concept
SLN	Sentinel lymph node
NPV	Negative predictive value
ECOG	Eastern Cooperative Oncology Group
ICG	Indocyanine Green
UPP	Upper paracervical pathway
LPP	Lower paracervical pathway
H&E	Hematoxylin and eosin
AJCC	American Joint Committee on Cancer
EORTC	European Organization for Research and Treatment of Cancer
QLQ	Quality of Life Questionnaire
HRQoL	Health related quality of life
RFS	Recurrence free survival
CI	Confidence interval
GCP	Good Clinical Practice
EDC	Electronic Data Capture
eCRF	Electronic case report form

TABLE OF CONTENTS

1 WHY THIS TRIAL IS NEEDED

FIGO staging in chapter 1 refers to staging manual before the latest revision in 2018.

1.1 BACKGROUND

Cancer of the uterine cervix is the fourth leading cause of cancer deaths in women and the fourth most common cancer in females worldwide, affecting 500 000 women annually.[1] In many developing countries, cervical cancer (CC) is the leading cause of cancer death and also the most commonly diagnosed cancer. In the industrialized world, the incidence and mortality is considerably lower, mainly as a result of effective screening programs where precancerous lesions are diagnosed and treated but also due to effective treatment.[2,3] In the Nordic countries, 1390 women are diagnosed annually and the incidence is rising.[4] In Sweden, 550 new cases of cervical cancer are diagnosed annually with a median age at diagnoses of 48 years with the highest incidence at ages 40 and 70.[5]

The presence of Human papillomavirus (HPV) infection is necessary but not sufficient in the carcinogenesis leading to cervical cancer.[6] Synchronous sexually transmitted disease, immunosuppression (e.g. HIV infection), long term use of oral contraceptives, high number of live births, smoking and increased number of sexual male partners are all factors associated with cervical carcinoma. [7,8]

Staging

Staging of cervical cancer according to the International Federation of Obstetrics and Gynaecology (FIGO) and was clinical until October 2018. [9] However, it has been demonstrated that clinical FIGO staging underestimates disease stage in 15-30% and 40% of women with early and advanced stage disease respectively as compared to surgical staging.[10-12] In the revised FIGO staging manual, imaging and histopathological evaluation may be included[13]. The latest FIGO staging is available in Appendix 17.1.

Prognosis

The total 5-year relative survival in the Nordic countries ranges between 58-67%.[4] Stage of disease at diagnosis strongly correlates to prognosis. In Sweden, 57% of women are diagnosed in early stage (stage ≤ IB1) of disease with a 5-year overall survival (OS) of >90%.[14] However, presence of lymph node metastasis deteriorates prognosis with a reported 75% overall 5-year survival.[15,16] Lymphatic or vascular space invasion (LVSI) of tumour, depth of tumour invasion

in the cervical stroma and size of tumour are also unfavorable prognostic factors.[17-19]

Treatment

Treatment of CC consists of surgery, radiotherapy and chemotherapy alone or in different combinations. Traditionally, surgery constitutes primary treatment of early-stage tumors with or without adjuvant treatment depending on prognostic factors. Advanced stage tumors are treated with primary radiotherapy with concomitant chemotherapy. [20,21]

1.1.1 Surgical Treatment

Ernst Wertheim described the radical hysterectomy with excision of parametria and pelvic lymph node removal in 1912, the procedure resulted in high mortality and morbidity.[22] Four decades later, Joe Vincent Meigs modified the procedure with parametrial resection to the pelvic side wall with addition of systematic pelvic lymph node dissection.[23] In addition to a very low operative mortality, a 90% and 63% 5-year overall survival was demonstrated for stage I and stage II respectively. Piver et al further modified the procedure in an attempt to further reduce morbidity and also classified the extent of the procedure (class I; removal of paracervical tissue including uterine vessels without dissecting into cervical tissue or mobilization of the ureter, class II; uterine artery is resected medially to the ureter after its mobilization, class III; uterine artery resected at its origin from the internal iliac artery).[24] The less radical surgical approach was further investigated with reassuring survival and reduced morbidity. [25,26] Landoni et al randomised 243 women with stage IB1 and IIA cervical cancer to either Piver class II or III radical hysterectomy.[18] There was no difference in 5-year OS (81 vs 77%) or disease free survival (DFS) (75 vs 73%) but less late morbidity was reported in the Piver class II group (13 vs 28% p=0.1). The proportion of patients who received adjuvant external beam radiation therapy (EBRT) was high but balanced (54 vs 55%).

There are other classifications of radical hysterectomy that have been proposed like the nerve sparing technique originating from Japan [27,28] that has further complicated the nomenclature of anatomic structures involved. In order to simplify classification, Querleu and Morrow proposed a system with four types of radical hysterectomy regardless of operation modality (type A-D) and in addition, a common nomenclature of the anatomic structures surrounding the uterine cervix. They describe type A being the least radical with only minimal paracervical tissue dissection and D being the most radical laterally and dorsally. [29,30] This system has gained

substantial popularity. The trend has been towards less radical surgery in stage IA disease, where simple hysterectomy and sentinel node is now according to the European Society of Gynaecological Oncology (ESGO) guidelines accepted instead of complete lymph node dissection with exception where LVSI is present .[21] In the recently published international SHAPE-trial, women with tumors <2cm (with less than 10 mm depth of invasion on LEEP/cone biopsy and/or <50% invasion on MRI) were randomized to radical hysterectomy (control) or simple hysterectomy (experimental), 700 women were recruited 2012-2019 and final analysis demonstrated non-inferiority for simple hysterectomy with significantly better morbidity profile[31]. These data will most likely have practice changing implications and it is reasonable to assume that women fulfilling the "SHAPE-criteria" no longer should be recommended radical hysterectomy.

In 2009, Hockel et al presented a novel surgical technique based on resection of embryological compartments, the Total Meso Metrial Resection (TMMR), where the lymphadenectomy described was very radical in contrast to a less radical hysterectomy. [32,33] In his study 212 women with stage IB1-IIB cervical cancer were prospectively followed after surgery with TMMR without adjuvant treatment. The 5-year OS and DFS was 96 vs 94% respectively despite omitting adjuvant treatment, which is exceptional. The results have yet to be reproduced.

In summary, despite efforts of standardizing surgery for patients with cervical cancer during the last decades, the anatomic-surgical definition of radical hysterectomy remains a challenge for the surgeon. However, there is consensus in the western world that surgery is gold standard treatment for early stage disease (≤ IB1 + IIA1) and radiation with concomitant chemotherapy for advanced stages ≥ IB2 (except IIA1). In Sweden, radical hysterectomy type B according to Querleu-Morrows classification is recommended for patients with stage IA2 with LVSI, type B or C for stage IB1 (type B or C) and type C for stage IIA.[34]

1.1.2 Minimally invasive surgery

In the 1990's the first experiences with laparoscopic (LS) radical hysterectomy (TLRH) with pelvic (PLND) and paraaortic lymphadenectomy (PALND) were published.[35-38] Despite promise of possible advantages, LS for cervical cancer did not gain strong acceptance.

The United States Food and Drug administration (U.S. FDA) approved robot-assisted laparoscopic surgery (RALS) for gynecologic procedures in 2005. RALS offers the three-

dimensional magnification vision, dexterity and possibly shorter learning curve and favorable ergonomics.[39] Shortly after introduction, the first case-report was published describing the feasibility of RALS to perform a Piver class III radical hysterectomy.[40] The uptake of RALS has been dramatic and observational studies have demonstrated that RALS is associated with shorter hospital stay, less blood loss and acceptable operation time (OT). [41-43] Furthermore, compared to conventional laparoscopy, OT is significantly shorter with RALS.[43]

Most observational studies on oncologic outcomes after RALS seem reassuring with no apparent differences in comparison with laparotomy (LT). [44-47]

The international LACC-trial[48], a multi-centre non-inferiority randomised controlled trial that started recruitment of women with early stage cervical cancer in 2008 with disease-free survival by LT or MIS as primary outcome was prematurely closed by the Data safety monitoring committee in 2017 before reaching planned accrual of 740 women. The final study population comprised 631 women with early-stage cervical cancer, randomized to either open radical hysterectomy (n=312) or MIS (n=319). In the MIS group, the majority of women were operated using conventional laparoscopy (84 %) whereas only 16 % by RALS. There were no differences in tumor size, histology, adjuvant treatment or patient characteristics. After a median follow-up of 30 months, MIS was inferior to LT with a hazard ratio (HR) 3.7 (95% CI 1.63-8.58) for recurrence and 6.0 (95% CI 1.77-20.3) for overall survival. The authors speculate that the use of intrauterine manipulators, the CO_2 gas or intra-corporeal colpotomy may account for the surprising outcomes. The results from the LACC-trial were in part supported by population-based data from the United States, demonstrating that MIS was associated with significantly worse survival than women treated with open surgery.[49]

In response to the unexpected LACC outcomes, a population based, nation-wide analysis based on data from the Swedish Quality Register for Gynecologic Cancer (SQRGC), was conducted. Preliminary results. demonstrate equal OS and DFS in women operated by RALS or LT between 2011-2017. The DFS of 87% for robotic surgery is in fact identical to the DFS in MIS arm of the LACC trial while the DFS for laparotomy group was 84%, both had a median follow up time of 44 months. [14]

1.1.3 Sentinel lymph node biopsy

The sentinel node biopsy concept (SNB) is well established in the surgical management of several malignancies including breast and vulvar cancer, with sufficient information gained on lymph node status for clinical decision making but with less morbidity. [50-52 53]

Pelvic lymphadenectomy in cervical cancer is an extensive diagnostic procedure with risk of lasting morbidity [54] It is estimated that 15% of women surgically treated for early stage disease have metastasis in the pelvic lymph nodes. [18,19,23] These women are subjected to additional adjuvant EBRT with substantially increased morbidity.[55,56] Undoubtedly, replacing PLND with SNB in cervical cancer would decrease morbidity.

Traditionally, radiotracers (Technetium) with or without augmentation of blue dye have been used for SNB. In patients with early-stage CC, the reported detection rate of sentinel lymph nodes (SLN) with blue dye only is unsatisfactory. However, when Technetium tracer is added, single center cohort studies suggest a unilateral detection from 75-100% and bilateral detection rate 66-72%, sensitivity reported 83-87% and a negative predictive value (NPV) of 95-97%.[57,58 59,60] Moreover, ultrastaging of SLN enhances detection of metastases with an increase of micro-metastases and isolated tumour cells[61,62]

The SENTICOL I multicenter cohort study, followed 139 women with early CC subjected to SNB (blue dye and technetium as tracer) by laparoscopy prospectively. [63] A sensitivity and negative predictive value (NPV) of 92 and 98% respectively was demonstrated. Moreover, the bilateral detection rate was 77%. The SENTICOL II randomised 200 women with early-stage CC to either PLND or SNB only with aim of evaluating postoperative short and long term complications. A significantly decreased morbidity in favour of SNB only was demonstrated, though final publication is awaited. [64]

In the most recent ESGO guidelines on cervical cancer, SNB is recommended in stage IA without LVSI. [21] There are small studies suggesting a high diagnostic accuracy of SNB even in larger tumors.[15,65]

The SENTICOL III RCT (ClinicalTrials.gov Identifier: NCT03386734), will start accrual this year with the aim to investigate the oncologic safety of SNB only vs PLND with 3-year DFS as primary outcome.

The SENTIX cohort study (ClinicalTrials.gov Identifier: NCT02494063), with ongoing prospective accrual of women with stage ≤ IB1 CC, aims to investigate the 2-year recurrence rate of women subjected to SNB only.

Indocyanine green (ICG), primarily used in MIS with near infra-red camera for detection, has been demonstrated to be superior in small series of patients with cervical cancer both regarding diagnostic accuracy and detection rate. [66] [67] [15]Larger prospective studies on ICG with near infrared fluorescence detection in patients with CC are lacking. Furthermore, the optimal dose and number of injections sites for ICG has not yet been established.

1.2 RATIONALE FOR STUDY

The standard surgical treatment for early-stage cervical cancer is radical hysterectomy with pelvic lymphadenectomy. During the past decade, RALS has replaced the open approach in the Nordic countries. The implementation of RALS has fundamentally changed Nordic health care with significant effects on infrastructure, health economy and surgical training. Novel technologies incorporated in the robotic platform enables improved lymph node assessment. The unexpected results from the LACC trial suggest that MIS no longer can be considered safe for the surgical management of early-stage cervical cancer. However, these outcomes contrast with nationwide, population-based data demonstrating equal outcomes between women treated with RALS or laparotomy.

The LACC trial has several important limitations:

- More than 80% of women in the MIS arm were treated with conventional laparoscopy. In the Nordic countries, conventional laparoscopy never gained acceptance and laparotomy remained the primary modality until the introduction of RALS. Whether RALS would result in different outcomes remains to be demonstrated.
- The LACC trial recruited participants from 33 centers worldwide during nine years. Although the protocol required accreditation of participating surgeons, internal validity can be questionned. This is supported by the fact that all recurrences in MIS arm were concentrated to 13 centers. In the Nordic countries, cervical cancer treatment is centralised to territiary referal centers (university hospitals), resulting in high-volume centers. In addition, radical hysterctomy is restricted to a limited number of sub-specialised surgeons.

- The LACC trial allowed any type of uterine manipulators, including intra-uterine devices. In the Nordic countries, only different types of vaginal probes (to delineate the fornices) are being used.

Taken together, the LACC trial does not reflect current practice in the Nordic countries. The health care systems have gradually been adapted to RALS and the perceived safety is supported by Nordic population-based studies. However, the LACC trial is currently the only RCT exploring the safety of MIS and to establish the safety of current practice, a new RCT is needed. Given the excellent outcomes in the open arm in the LACC trial, it is unlikely that RALS can generate superior outcomes. It is therefore reasonable to design a new RCT as a non-inferiority trial.

2 STUDY OBJECTIVES

2.1 HYPOTHESIS

Robot-assisted laparoscopic radical hysterectomy with pelvic lymphadenectomy is non-inferior to laparotomy in recurrence free survival with the advantage of shorter hospital stay, postoperative complications and lower health care costs in a public health care system.

2.2 PRIMARY OBJECTIVE

The less invasive surgical modality, robot assisted laparoscopic surgery, has become standard of care in the Nordic countries for treatment of early stage cervical cancer without any trial supporting its safety or superiority over laparotomy. This trial aims to compare the oncologic safety of RALS to conventional laparotomy.

2.3 SECONDARY OBJECTIVES

To evaluate overall survival, intra- (including validation of proposed intraoperative classifications) and postoperative outcomes 30 days after surgery, health care costs, quality of life and lymphoedema and the diagnostic accuracy of pelvic sentinel lymph node biopsy concept in women with early stage cervical cancer.

2.4 PRIMARY OUTCOME MEASURE

5-year recurrence-free survival

2.4.1 Definition of primary outcome measure

Recurrence-free survival time (RFS) is defined as the time-interval between the date of randomisation and the date of recurrence or to the date of death (according to STEEP[68]). For recurrence-free patients still alive, RFS time is calculated from the date of randomisation to the date of last clinical visit.

A clinical or by imaging suspicion of recurrence of disease has to be verified by histopathological assessment.

The date of biopsy will be the date of recurrence (or date of death).

2.4.1.1 Local recurrence

Vaginal or pelvic side-wall (including nodal recurrence)

2.4.1.2 Distant recurrence

Extra-pelvic lymph nodes, port site metastases, parenchymatous organ, carcinomatosis, bone metastases

2.5 SECONDARY OUTCOME MEASURES

- Overall survival
- Health related quality of life including lymphoedema
- Intraoperative complications
- Postoperative 30 complications
- Diagnostic accuracy of the pelvic sentinel lymph node concept
- Health care costs

2.5.1 Definition of secondary outcome measures

Overall survival (OS): Survival time is calculated from the date of randomisation to the date of death (due to any cause), or for patients still alive to the date of last clinical follow-up or contact.

Health related quality of life (HRQoL): will be assessed by questionnaires completed by study participants preferably as electronical patient reported outcome measures or during the clinic visit (by manually filling in forms, by accessible computer or by mail). The assessments are performed before randomisation (baseline), 1 month, 6 months, 1 year, 2 years and 5 years after surgery. Questionnaires comprise the EORTC QLQ-30, QLQ-CX24, LYMQOL and Eq5D-3L (see Appendix 17.8,17.9,17.10,17.11).

Intraoperative complications: Defined according to Kaafarani et al and the CLASSIC classification (see Appendix 17.4).

Postoperative 30-day complications: According to the Clavien-Dindo classifications (see Appendix 17.2)

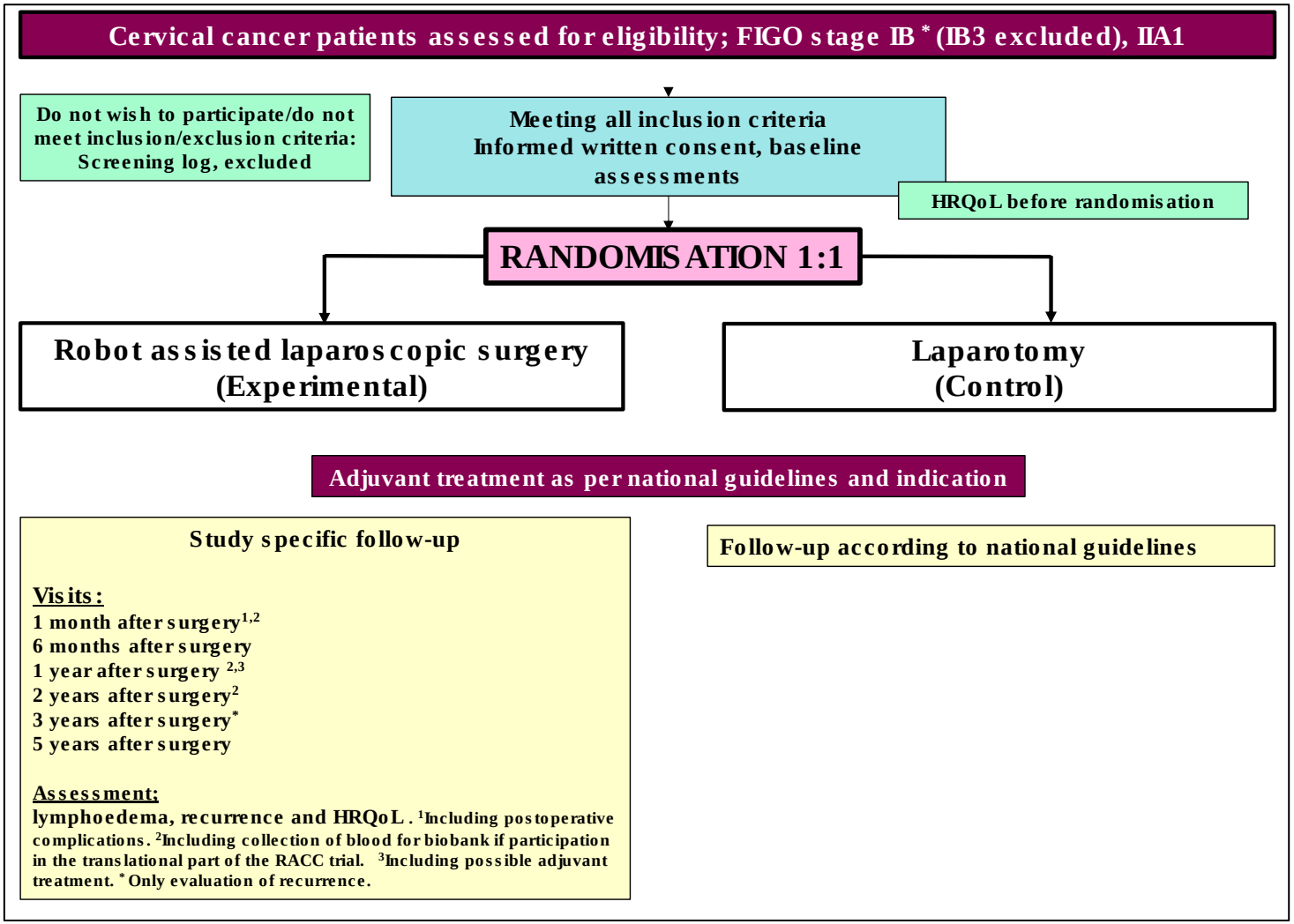
Diagnostic accuracy of the pelvic sentinel lymph node concept: Sensitivity and negative predictive value of the sentinel lymph node specimen (in mapped women) and the sentinel lymph node algorithm. In addition, the uni and bilateral mapping rate.

Health care costs: At the discretion of the chair of the sub-committee on health care costs. Direct costs will be used by assessing internal accounting and billing systems within the hospitals. We will also measure the quality-adjusted life years (QALYs) gained with the intervention and use this to undertake a cost-utility analysis. The QALY calculations will be based on health status measures for trial participants, with valuations of changes in health status and quality of life based on the EQ-5D.

3 STUDY DESIGN

Randomised controlled non-inferiority trial.

3.1 STUDY SCHEMA



*After the results of the SHAPE trial, the inclusion of stage IB and IB1 is up to the investigators discretion.

3.2 SCHEDULE OF EVENTS TABLE

Procedures	Enrolment/Baseline	Enrolment*	Surgery	Postoperative day 1	Clinical visit 1- month after surgery	Clinical visit 6 months after surgery	Clinical visit 1 year after surgery	Clinical visit 2 years after surgery	Clinical visit 3 years after surgery	Clinical visit 5 years after surgery	At time of eventual recurrence
Informed consent oral and written	X										
Demographics	X										
Randomisation		X									
Record surgical procedure performed and localization of sentinel lymph node			X								
Record per-operative complications[2]			X								
Length of stay					X						
Record 30-day post-operative complications[3]					X						
Record final pathology					X						
Record adjuvant treatment							X				
Collection of blood for biobank[4]	X			X	X	X	X	X			X
Collection of urine[4]	X				X	X	X	X			X
Collection of peritoneal biopsies and blood, site Karolinska only			X**								
Collection of wet-smear from cervix (Thin-prep)[4]			X								
Quality of life questionnaires[1]	X				X	X	X	X		X	
Lymphoedema[5]	X				X	X	X	X		X	
Record if recurrence						X	X	X	X	X	

[1]EORTC-QLQ-C30 + CX24, Eq5D-3L. [2]According to Classic and Kaafarani see Appendix 17.4. [3]According to Clavien-Dindo classification, by review of hospital charts, contact with patient at visit or per telephone, see Appendix 17.2. [4]Not mandatory for centers not participating in the translational part of the study. [5] Lymphatic side effects according to the CTCAE 3.0, see Appendix 17.2 and LYMQOL Questionnaire, see Appendix 17.10 *may only be used by centres in which the questionnaire's translation has been validated.* * Randomisation only after completed quality of life questionnaires. **Pelvic peritoneal biopsies and blood at the beginning and end of the surgical procedure.

4 STUDY ENROLLMENT

4.1 SCREENING PROCEDURE AND PARTICIPANT IDENTIFICATION

All women with histologically proven cervical cancer, FIGO stage IB (IB3 excluded), IIA1 can undergo screening for this trial and will be documented in a screening log. After obtaining oral and written informed consent, patients will be registered and randomised. Registration data has to be entered to an electronic Case Report Form (eCRF).

4.2 INCLUSION CRITERIA

- Histologically confirmed primary adenocarcinoma, squamous cell carcinoma or adeno-squamous carcinoma of the uterine cervix;
- Women with histologically confirmed FIGO stage IB (IB3 excluded) and IIA1 disease. It is at the discretion of local principal investigators to decide if tumours fulfilling the SHAPE-criteria should be considered an exclusion criterion (pending revisions of national and international guideline recommendations).
- Women undergoing either a Type B or C radical hysterectomy according to Querleu Morrow classification
- ECOG Performance Status of 0, 1 or 2
- Patient must be suitable for surgery.
- Patients who have signed an approved Informed Consent
- Age> 18 years

4.3 EXCLUSION CRITERIA

- Any histology other than adenocarcinoma, squamous cell carcinoma or adeno-squamous carcinoma of the uterine cervix
- Tumour size greater than 4 cm, estimated by either magnetic resonance imaging (MRI) or clinical examination
- FIGO stage II-IV (except IIA1). It is at the discretion of local principal investigators to decide if tumours fulfilling the SHAPE-criteria should be considered an exclusion criterion (pending revisions of national and international guideline recommendations).
- Women with a history of pelvic or abdominal radiotherapy
- Women who are pregnant
- Women with contraindications to surgery
- Women with evidence of metastatic disease by conventional imaging studies, enlarged pelvic or aortic lymph nodes > 2cm; or histologically positive lymph nodes
- Serious concomitant systemic disorders incompatible with surgery or study (at the discretion of the investigator)
- Women unable to withstand prolonged lithotomy and steep Trendelenburg position

- Women with secondary invasive neoplasm in the last 5 years (except non-melanoma skin cancer, breast cancer T1 N0 M0 grade 1 or 2 without any signs of recurrence or activity)
- Women with iodine allergy cannot be part of the sentinel node part of the trial but are allowed randomisation as to the primary outcome

4.4 RANDOMISATION

After verification of eligibility, signed informed written consent and baseline HRQoL questionnaires completed, patients will be randomised to either robot assisted laparoscopic surgery or laparotomy by equal allocation, 1:1. The randomisation procedure will be pre-stratified for participating centre (permuted block design).

Randomisation will be performed centrally by the Clinical Trials Unit at Center for Clinical Cancer Studies, Theme Cancer, Karolinska University Hospital, Stockholm, Sweden. Randomisation will only be performed if the investigator confirms completed baseline HRQoL questionnaires. All inclusion criteria and no exclusion criteria must be met. At the time of inclusion, inclusion and exclusion criteria are entered into the randomization/registration application, which is a web-based instrument (ALEA). Username and password are required to log in; each investigator authorized to register patients has a personal login user name and password. If all criteria are met, patients are registered, and the allocated patient number is recorded in the patients' medical file.

4.5 DEFINITION END OF TRIAL

The study will end when all patients enrolled in trial have been followed for 5 years, died, withdrawn consent or are lost to follow-up. The trial steering committee may end enrolment at any time if it is deemed that this is in the best interest of the patients.

5 STUDY TREATMENT

The surgical procedure between treatment arms do not differ except for which surgical modality (RALS or LT).

5.1 EXPERIMENTAL TREATMENT

- Radical hysterectomy, Type B or C according to the Querleu Morrow classification,

(± salpingoophorectomy, ± salpingectomy) with pelvic lymphadenectomy after pelvic sentinel lymph node mapping and biopsy (± paraaortic lymphadenectomy at the institutions discretion) by robot-assisted laparoscopic surgery.

5.2 STANDARD/CONTROL TREATMENT

- Radical hysterectomy, Type B or C radical hysterectomy according to Querleu Morrow classification, (± salpingoophorectomy, ± salpingectomy) with pelvic lymphadenectomy after pelvic sentinel lymph node mapping and biopsy (± paraaortic lymphadenectomy at the institutions discretion) by laparotomy.

5.3 SURGICAL PROCEDURE

The surgery starts with injection of tracer in the uterine cervix and SLN biopsy (as defined in 5.4). *For RALS, an intrauterine manipulator is not allowed.* A vaginal probe/manipulator to delineate the vaginal fornices is allowed. Measures to avoid tumour spillage prior to colpotomy (by either modality) is mandatory. Type of measure is at the discretion of the local PI.

The abdomen is then entered at the discretion of the surgeon, the salpinx is closed by coagulation. After extirpation of the sentinel nodes the pelvic lymphadenectomy is performed followed by the radical hysterectomy. In case of leaving the ovaries in situ it is recommended that the salpinges are extirpated.

If surgery is performed by RALS the lymph nodes are retrieved via endo-catch or other specimen retrieval bags and the hysterectomy specimen is retrieved via the vagina.

5.3.1 Definition of radical hysterectomy

The extent of radicality according to the Querleu & Morrow classification should be based on tumor characteristics and national guidelines. The following types (Table 1) of radical hysterectomy is allowed in the trial. [30,69]

Table 1

Type	Lateral parametrium	Ventral parametrium	Dorsal parametrium
B1	At the ureter	Partial excision of the vesicouterine ligament	Partial resection of the rectouterine-rectovaginal ligament and uterosacral peritoneal fold

B2	Identical to B1 plus paracervical lymphadenectomy without resection of vascular/nerve structures	Partial excision of the vesicouterine ligament	Partial resection of the rectouterine-rectovaginal ligament and uterosacral peritoneal fold
C1	At the iliac vessels transversally, caudal part is preserved	Excision of the vesicouterine ligament at the bladder. Proximal part of the vesicovaginal ligament	At the rectum (hypogastric nerve is dissected and spared)

5.3.2 Definition and anatomical boundaries for pelvic (and paraaortic) lymphadenectomy

Pelvic lymphadenectomy is defined as resection of all fatty tissue and lymph nodes in lymph node compartment 1 to 4, See Table 2.

Table 2

Anatomical boundaries of lymph node compartments				
Lymph node compartment	**Cephalad limit**	**Lateral limit**	**Caudad limit**	**Medial limit**
External iliac area	Bifurcation of external and internal iliac artery	Genitofemoral nerve	Cloquet's lymph node	External iliac vein
Obturator fossa	Internal iliac vein	Iliopsoas muscle	Os pubis, obturator nerve	Obliterated umbilical artery
Common iliac	Aortic bifurcation	Genitofemoral nerve	Bifurcation of external and internal iliac artery	Common iliac artery
Pre-sacral	Aortic bifurcation	Common iliac artery	Lower promontory	Hypogastric nerve (as distinction between right and left)
Lower paraaortic	Inferior mesenteric artery	Ureter	Aortic bifurcation	
Higher paraaortic	Left renal vein	Ureter	Inferior mesenteric artery	

5.3.2.1 Labelling of lymph node specimens for histopathology review

- Right pelvis: External iliac, obturator fossa, common iliac
- Left pelvis: External iliac, obturator fossa, common iliac
- Pre-sacral: Left, Right

- (Lymph nodes above the inferior mesenteric artery (higher paraaortic))
- (Lymph nodes below the inferior mesenteric artery (lower paraaortic))

The specimens are sent to for histopathological review labelled according to Appendix 17.5.

5.4 SENTINEL NODE BIOPSY

For centers outside Sweden, participation in the sentinel node biopsy part of the trial is optional.

If international centers choose to participate in this part of the trial it is at the respective institutions discretion to choose dye tracer with or without radiotracer. However, it is vital that the same method is used in both randomisation arms and adherence to 5.4.3 in case of non-mapping. The sentinel lymph nodes must be assessed by ultrastaging according to institutional protocol. Moreover, frozen section of sentinel lymph nodes is not allowed.

International centers are encouraged to participate in the full sentinel node biopsy algorithm of the RACC trial, which requires on-site training by the members of Trial Steering Committee.

5.4.1 Surgical procedure (RACC-trial ALGORITHM)

The abdominal part of the procedure starts with identification and extirpation of the sentinel lymph nodes. The sentinel lymph node biopsy procedure is described as follows and below must be adhered to. The description is applicable for both randomisation arms.

Injection of tracer in the uterine cervix, for details on dilution, dose and injection of ICG, see Appendix 17.6. For women randomised to RALS, a fornix presenter *without an intracervical device* is then adapted around the cervix. After entering the abdomen fluorescence imaging using the FireFly® Mode is utilized. The transperitoneal display of afferent lymphatic pathways from the uterine cervix is to be identified bilaterally. The two pathways comprise the upper paracervical pathway (UPP) (along the uterine artery to the external and obturator nodes, continuing lateral to the common iliac artery to the inframesenteric paraaortic nodes) and the lower paracervical pathway (LPP) (medial to the internal iliac artery to the internal iliac and presacral nodes and continuing medial to the common iliac artery to the inframesenteric paraaortic area) according to Geppert et al[70], see Figure 1.

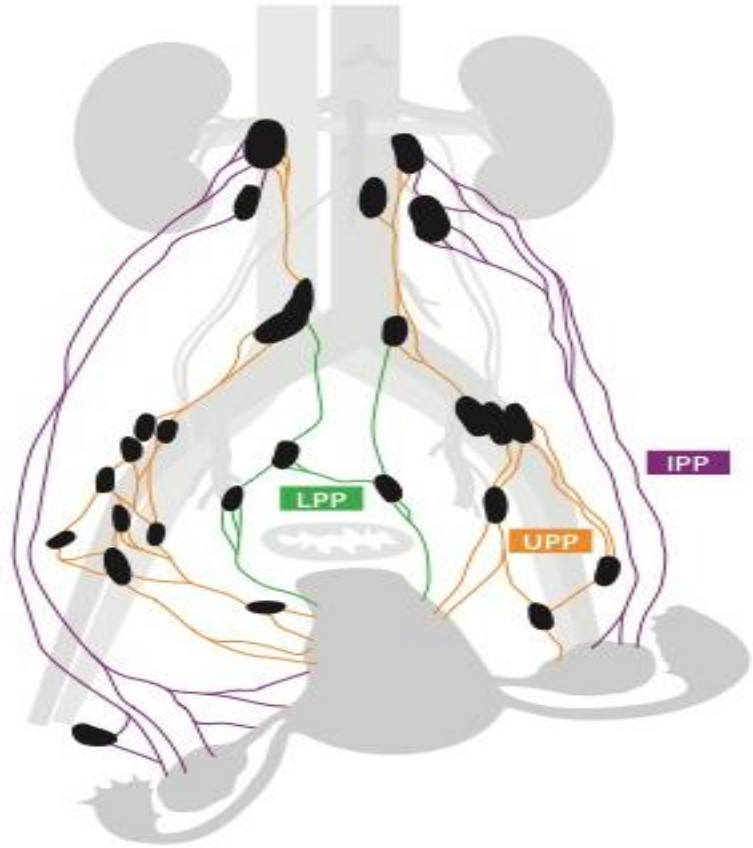


Figure 1

If a pathway is not visualized through the peritoneum, the avascular presacral, paravesical and pararectal planes are opened, keeping the lymphatic vessels intact. In case of non-display in any pathway after 10 minutes, an ipsilateral re-injection at 3 or 9 o'clock of 0,25ml of the ICG-solution is performed if ICG is used. Display of pathways after the first and if needed the second injection is registered in the study case report form. A **SLN type 1** is defined as the juxta-uterine ICG/tracer positive node with an afferent ICG positive lymph vessel in the UPP and LPP respectively on each pelvic sidewall with the potential of parallel lymphatics in the UPP to the external, common iliac and obturator areas. In case of an ICG positive pathway with no ICG positive nodes, the node draining the ICG positive lymphatic channel was defined as **SLN type 2**.

Nodes macroscopically suspect of metastatic disease are defined as **SLN macro** regardless of ICG uptake although ICG positivity or negativity is noted in the study file. *These nodes are allowed to be sent for frozen section as per usual.* To avoid visual obstruction by ICG-leaking, SLNs is first removed along the LPP, see Figure 1.

The positions and types of SLNs are graphically illustrated by the surgeons during surgery on an anatomical chart. Following identification and removal of SLNs, a pelvic lymphadenectomy is then performed. (see Appendix 17.5)

Frozen section of the sentinel lymph nodes during surgery is not allowed.

The sentinel lymph node specimens are labelled and sent for histopathological review according to Appendix 17.5

New methodologies that may be introduced as routine procedure during the course of the study are also permitted, provided that the reliability is proven. Approval of new methods can only be granted by the study steering committee (coordinating investigators and trial steering committee).

In the laparotomy group a robotic endoscope with fluorescence imaging using the FireFly® Mode is utilized in the same manner as in the RALS group. If suffice funding is granted for the RACC trial, it is the aim of the coordinating investigator to provide each participating site with an Xi light weight robotic endoscope for this purpose only during the course of the RACC trial. If a participating centre have access to near infra-red endoscope for traditional laparoscopy, they are of course allowed.

5.4.2 Sentinel lymph node algorithm (RACC-trial ALGORITHM)

The sentinel lymph node algorithm includes;

- Assessment of the UPP and LPP in both hemi-pelvises
- Reinjection of ICG tracer, if used, in the uterine cervix in case of uni- or bilateral non-display.
- Resection of all macroscopic suspicious lymph nodes regardless of mapping success or not.

5.4.3 If sentinel lymph node mapping fails (ANY ALGORITHM)

To avoid uneven distribution of ultrastaging between the treatment arms due to possible higher mapping rate of sentinel lymph nodes in any of the arms and thus possible uneven detection of micro-metastases, it is of utmost importance that below is adhered to.

In case of uni or bilateral mapping failure, "sampling" of lymph nodes in the previously most commonly described anatomic-topographic location of sentinel lymph nodes is performed, either uni or bilaterally[62,71]. Unpublished data from Persson and colleagues (Lund, Sweden) utilising ICG as tracer for detection of SLN is the basis of the anatomic locations that should be "sampled" in the RACC trial, see Figure 3.

The "sampled" lymph nodes are labelled as **SLN-sampling** and graphically illustrated by the surgeons during surgery on an anatomical chart just as the other sentinel lymph nodes (Appendix 17.7) and are also subjected to ultrastaging.

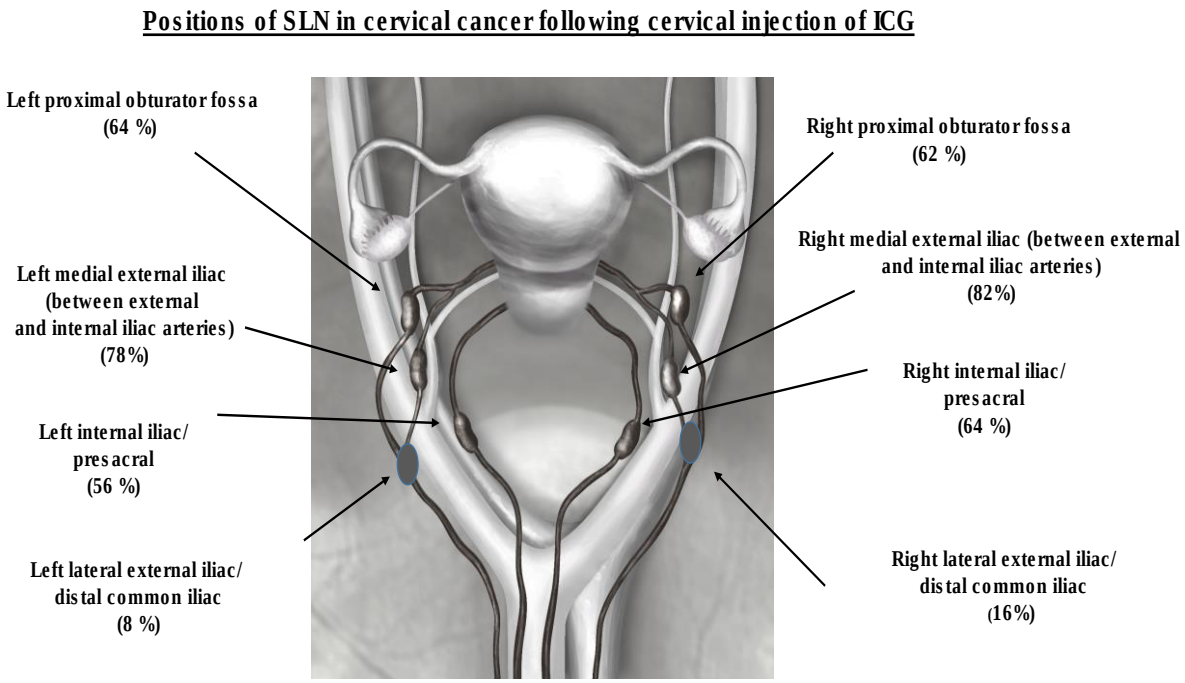
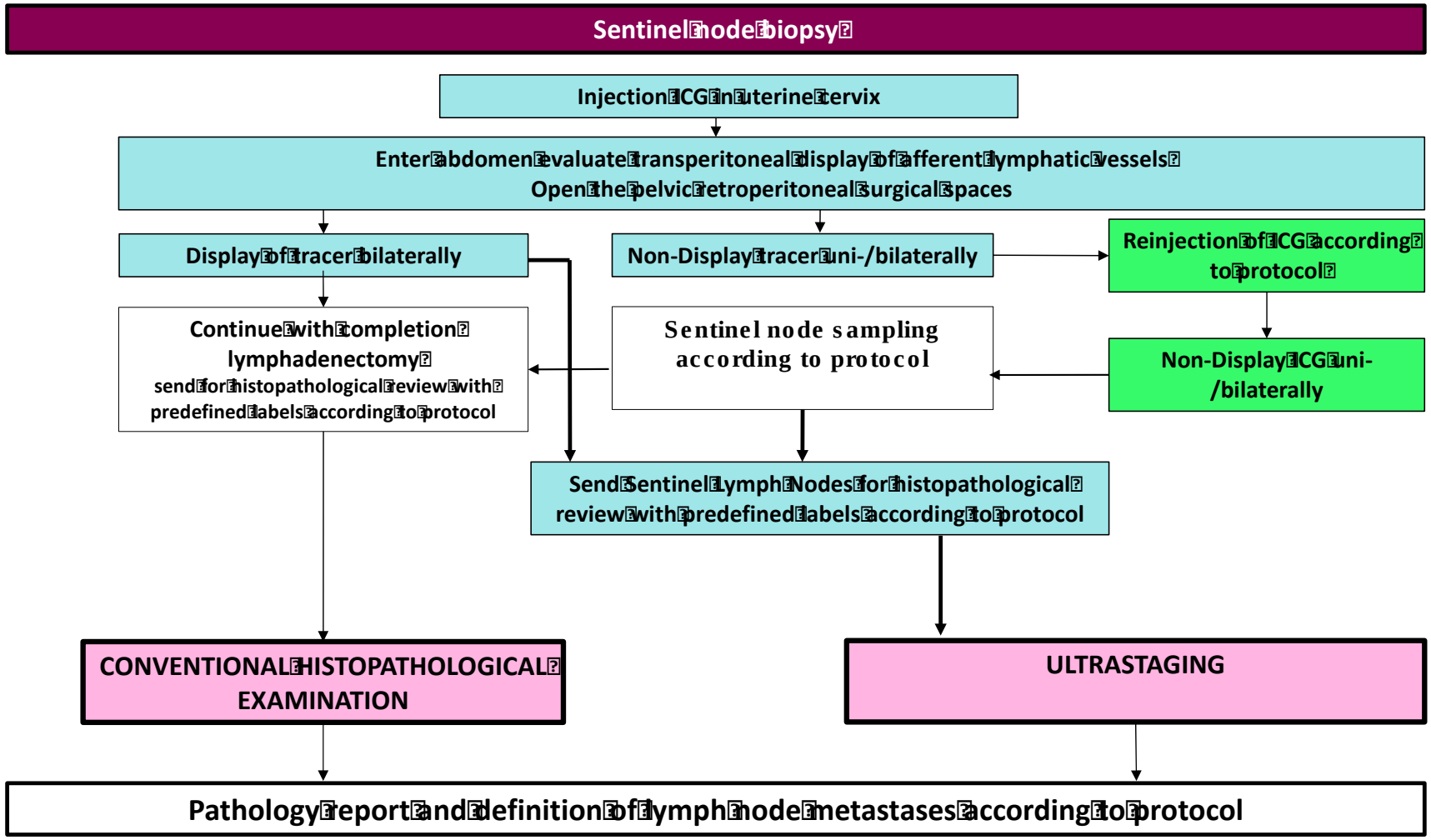


Figure 2

5.4.4 Schema for sentinel node biopsy (RACC-trial ALGORITHM)



5.5 ADJUVANT TREATMENT

It is of utmost importance that adjuvant treatment is adhered to according to national or institutional guidelines, each participating centre will disclose indication for and schema of adjuvant treatment in the site identification and quality assessment form (see Appendix 17.7)

Patients enrolled in the RACC trial can be enrolled in other trials on adjuvant medical oncologic treatment. However, it is crucial, that these protocols are **open for ALL patients** from both treatment arms.

6 EVALUATION OF HISTOPATHOLOGY

6.1 HYSTERECTOMY SPECIMEN

Hysterectomy specimens will be received and cut in according to the clinical routine at each of the participating centres. No adjustment of routine specimen management is required for the trial.

6.2 LYMPH NODES SPECIMENS

6.2.1 Non-sentinel lymph nodes

All macroscopically identified lymphoid tissue is embedded and, if the minimum thickness exceeds 3 mm, bisected and stained for hematoxylin and eosin (H&E).

6.2.2 Sentinel lymph nodes

All macroscopically identified lymphoid tissue is embedded and bisected if the minimum thickness exceeded 3 mm and stained for H&E, if negative for metastasis, ultrastaging is performed.

Ultrastaging using H&E staining is performed in five sections at three different levels, 200 µm apart, if the maximum diameter of the sentinel node tissue exceeded 1 mm. Immunohistochemistry (IHC) with staining for a cytokeratin marker, (for example pan-cytokeratin, cytokeratin MNF 116, AE1/AE3) is performed on the last, deepest level.

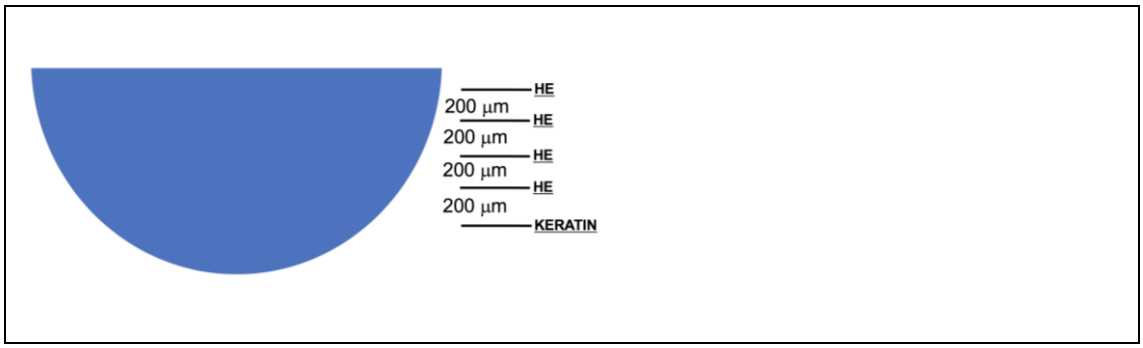


Figure 3. Schematic illustration of ultrastaging protocol. The first level can be taken as part of an initial evaluation and then the deeps levels after, or all the levels can be cut at once.

6.2.3 Definition of lymph node metastases

- Macro-metastases = tumour greater than 2.0 mm in diameter.
- Micro-metastases = tumour cell aggregates between 0.2 and 2.0 mm in diameter.
- Isolated tumour cells = individual tumour cells or aggregates that are less than 0.2 mm in diameter, usually detected by immunohistochemistry and less then 200 cells. ***(e.g. if less than 0.2 mm but more than 200 cells (or vice versa) = micro metastases).***
- Tumour absent – no tumour cells identified in H&E (or immunohistochemically, if applicable) stained sections.

The classification is according to American Joint Committee on Cancer (AJCC) staging for axillary nodes in breast cancer. [72]

6.3 PATHOLOGY REPORT

6.3.1 Hysterectomy specimen

Standard parameters in cervical cancer must be reported in the pathology report. Standard pathology reporting includes current, relevant prognostic histopathologic variables such as tumor type and grade, tumor size, tumor extension, resection margin status, presence or absence of lymph vascular invasion, and status of the vaginal manchette and parametria.

6.3.2 Lymph node specimen

Number of lymph nodes and metastatic lymph nodes per anatomic station 1-4 must be reported (see 5.3.2)

Number of sentinel lymph nodes and metastatic sentinel lymph nodes per anatomic station must be reported. In the event of no identified lymph nodes in the sentinel lymph node specimen, (“empty packet”) this must be reported

6.4 QUALITY ASSURANCE HISTOPATHOLOGY

All specimens must be evaluated/re-reviewed by the local gynecologic reference pathologist before entering data in the eCRF.

7 TRANSLATIONAL RESEARCH COMPONENT

The study will include a translational research component, which will have its focus on developing and validating novel biomarkers for prediction of lymph node status, prediction of recurrence risk and evaluation of therapy response.

Biomarkers

To date there are no available surveillance biomarkers to predict recurrence of patients treated for cervical cancer. As infection with high risk Human Papilloma Virus (HrHPV) is a necessary trigger for cancer growth in the uterine cervix, HPV-DNA is incorporated into the cervical epithelial cells during the process. All human cells go through natural cell death where DNA is continuously released into the blood by both healthy cells (cfDNA) and tumour cells (ctDNA). These fragments are finally rinsed from the body in the urine. By this mechanism ctDNA in blood or urine is a possible biomarker for cancers, moreover hypothetically HPV ctDNA is a specific marker for women with cervical cancer.

This part of the study is solely executed in Sweden where the primary aim is to examine the HPV ctDNA in women with early stage cervical cancer. Specific aims:

1. Exploratory analysis of the dynamics of HPV ctDNA over time
2. To test the hypothesis that HPV ctDNA is a predictor of treatment failure and recurrent disease and could be used to tailor postoperative surveillance.

Blood samples will be collected at 5 different time-points and urinary samples at 4 different time points (see Schedule of events table 3.2) as well as at the time of eventual recurrence of the disease. In addition, a liquid based cervical sample will be obtained prior to surgery to map the presence of HPV.

In addition, tumour material will be prospectively collected from surgical specimen to allow for molecular tumour characteristics to be further correlated with clinically relevant endpoints.

Peritoneum, site Karolinska only

To examine the direct effect of the Carbon dioxide (CO_2), used to insufflate the abdomen during laparoscopic surgery, on the peritoneal membrane. Small peritoneal biopsies (2x1 cm) from the broad ligament/pelvic peritoneum will be collected at the beginning and end of surgery as well as blood samples. The samples will be evaluated for mesothelial damage, invasion of tumour, inflammation and chemotherapy resistance, by an already established clinic to laboratory tissue handling protocol and ex-vivo model used in ovarian cancer.

8 RADIOMICS

Radiomics is a high-throughput approach to translate medical images into minable data by extracting a large number of quantitative features describing tumor intensity, shape and texture. In this sub-study of the RACC trial we hypothesize that radiomics features, being a robust quantification of imaging phenotypes, will potentially add layer in early and accurate radio genomics diagnosis, prognostication and treatment stratification in cervical cancer.

This sub-study is chaired by site Policlinico Agostino Gemelli IRCCS, Rome, Italy. Participation in this part of the RACC trial is optional for other participating sites. Sharing of data (images) will be pseudonymized through a secure central server.

Additional inclusion criteria inclusion in this sub-study:

- Availability of technically adequate routine staging imaging: 1.5 or 3.0 T MRI or ^{18}FDG-PET-CT

Additional exclusion criteria in this sub-study

- Absence or technical inadequacy of routine staging imaging (1.5 or 3 T MRI or ^{18}FDG-PET-CT)

For full protocol of this sub-study see Appendix 17.13

9 QUALITY ASSURANCE OF SURGERY

9.1 PARTICIPATING CENTERS

A site quality assessment form (see Appendix 17.7) including, institutional experience with RALS, annual volume of surgical gynecologic oncology cases and cervical cancer must be completed. In addition, 10 anonymized surgery reports from both radical hysterectomies and advanced ovarian cancer primary surgeries accompanied by their histopathology reports within 24 months has to be sent to the trial steering committee for review. Moreover, surgical variables (e.g. operation time, blood loss) and complications within 30 days after surgery according to Clavien Dindo must be reported (see Appendix 17.7). Furthermore, the infrastructure to participate in the trial must be satisfactory and data on institutional algorithm and indication for adjuvant treatment and what it constitutes must be reported. The total annual case-load of robotic procedures per site must exceed 100. In addition, the institution's ability to perform ultrastaging is considered.

If sentinel lymph node biopsy with ICG tracer is not an established procedure the Sub-committe on Sentinel lymph node biopsy and/or Trial Steering Committee will arrange on-site training.

During the study, it is at the discretion of the coordinating investigators and Trial steering committee to close centres with a higher than average rate of postoperative major complications or poor quality of surgery, from further accrual, temporarily of irrevocably after consultation with the Data Safety Monitoring Board.

9.2 PARTICIPATING SURGEONS

All included surgeons outside the primary investigating centre must be approved by the coordination investigators/s ensuring adherence to protocol. In the site identification and quality assessment form the participating surgeons experience and annual case-load will be reported for review. It is at the discretion of the coordinating investigators to select or deselect individual surgeons from participating in the trial. Audits on site or videos of procedures can be requested at the discretion of the coordinating investigators. Only surgeons stated in the Quality assessment form (see Appendix 17.7) are allowed being lead surgeons, amendments during the trial can be made.

9.2.1 Robot-assisted laparoscopic surgery

All included surgeon must have a previous experience of at least 20 radical hysterectomies and pelvic lymphadenectomies.

9.2.2 Laparotomy

All included surgeons must have a previous experience of at least 20 pelvic lymphadenectomies and an annual case load of at least 10 surgeries for advanced pelvic surgery including pelvic lymphadenectomy. Previous experience of at least 10 open radical hysterectomies is mandatory.

10 PATIENT REPORTED OUTCOMES (PROS)

Women with early-stage CC are relatively young with high chance of long-term survival. Recurrences are most prevalent within 2 years after treatment and conditional survival after 5 years is excellent. [73] For this reason, it is of utmost importance to offer affected women the treatment that causes the least possible late side-effects. Patient reported outcome measures

are used to evaluate incidence and grade of late effects related to the standard and the experimental arm. A special focus will be on late side-effects related to para-sympathetic nerve injuries, e.g., bladder and sexual dysfunction in addition to lymphoedema, physical-, emotional, and role functioning, fatigue and pain. One of the secondary aims of the RACC trial is therefore to compare patient-reported outcomes measures, i.e. patients' HRQoL between the treatment arms in the short-, long- and term. All women included in the RACC trial will be asked to answer the questionnaires.

10.1 POINTS OF ASSESSMENT

Baseline assessment will be obtained prior to randomisation and thereafter prospectively 1 and 6 months' post-surgery. Long-term effects will be assessed after 1, 2 and 5 years. The assessments will be made at time of out-patient visit.

10.2 INSTRUMENTS

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30, version 3.0 (EORTC QLQ-C30) is a HRQoL instrument developed to be multidimensional in structure and self-administrative to be used in clinical cancer trials.[74] It includes nine multi-item scales and six single item variables. The five functional scales consist of physical- (PF), role- (RF), emotional- (EF), social- (SE), and cognitive functioning (CF). Fatigue (FA), nausea/vomiting (NV) and pain (PA) comprise the three multi-item symptom scales. Additional symptoms are assessed by single items: dyspnoea (DY), sleep disturbances (SL), appetite loss (AP), constipation (CO), and diahorrea (DI). One single item scale concern financial problems related to disease and treatment. Most items are responded to on a four-point Likert scale ranging from 1 (not at all) to 4 (very much). The two items assessing global health and overall quality of life are responded to in seven categories ranging from 1 (very poor) to 7 (excellent).

The EORTC QLQ Cervical Cancer Module (CX-24) is a cervical cancer specific questionnaire developed and validated for use in women with cervical cancer .[75] It comprises 24-items divided into four functioning scales: Body image (CXBI), sexual activity (CXSXA), sexual enjoyment (CXSXE), Sexual/vaginal functioning (CXSV); and four symptom scales: symptom experience (CXSE), lymphoedema (CXLY), peripheral neuropathy (CXPN), menopausal symptoms (CXMS), sexual worry (CXSW). The questionnaire has been validated in an international study.[75] Completion of the questionnaire

takes about 15min. The items are responded to in the same four categories as most items in the EORTC QLQ-C30.

The generic and disease-specific EORTC questionnaires are supplemented by 10 screening items on lymphoedema in the legs, the genital- and the inguinal region. These items derive from the EORTC item bank and has been developed and validated (and translated) with the contribution of patients from the Nordic countries. These items are supplemented by the Lymphedema Quality of Life Questionnaire[76] (LYMQOL) which is a validated condition-specific quality of life assessment tool, ie. to be completed only if the patient report that she has lymphoedema. The LYMQOL assesses the impact of lymphoedema on several aspects of the patient's life. The LYMQOL has been forward-backward translated to several languages. LYMQOL may only be used within the RACC study by centers in which the questionnaire's translation has been validated.

EQ-5D is a standardized non-disease specific instrument for describing and valuing HRQoL, developed by the EuroQoL group [77]. It includes five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) with three levels of responses each (no problems, some problems or extreme problems). The EQ-5D also comprises a 20cm visual analogue scale (VAS) ranging from 0 (worst imaginable health state) to 100 (best imaginable health state) on which the respondent rates the current health. The index-based score is interpreted along a continuum where 1 represents best possible health and 0 represents dead. Some health states are given a figure below zero (worse than death).

10.3 PROCEDURE

First questionnaire: Before inclusion in the study, the patient is informed orally and in writing about the HRQoL assessment. The first questionnaire is completed before information is conveyed about to which arm the patient have been randomization.

Subsequent questionnaires will be collected in connection to the visits at the clinic/electronically/per conventional mail. The instruments will be given to the patient in the appropriate language for the site. The treating physicians will not have access to the HRQoL-forms. Completed questionnaires are always considered source document and must be filed accordingly.

11 HEALTH ECONOMICS

Health economics will be analyzed with respect to Swedish conditions first and, if comparable data is achieved, with an international perspective.

11.1 DIRECT COSTS

To assess the health care costs, the internal accounting and billing systems within the hospitals will be used as an estimate of direct costs based on the Cost Per Patient (CPP) principles for treatments separately[78]. Furthermore, the quality-adjusted life years (QALY) will be calculated based on data for the EQ-5D-instrument (for description see chapter 9.2). Variations of changes in health status and quality of life will serve for a cost-utility analysis and the results can be presented as an incremental cost-effectiveness ratio (ICER) and give an answer to the question of how much another year with full health will cost with the new method compared to the control arm. The long-term cost-effectiveness will be assessed with decision analytical models such as Markov models, which allows for a life-long comparison of the two treatment arms.

11.2 INDIRECT COSTS

For measuring indirect costs to disease, the two study arms will be analyzed in respect to estimation of productivity costs i.e., level of fall in production, where methods such as the friction cost method can be used[79]. The health economic analysis will be presented both with and without fall in production, to justify the data for patients aged over 65 years.

12 STATISTICAL CONSIDERATIONS

12.1 DATA ANALYSES

12.1.1 Primary endpoint

Recurrence-free survival time will be calculated from the date of randomization to the date of local recurrence, the date of distant recurrence or date of death (any cause), whichever comes first. For event-free patients, survival time will be calculated from the date randomization to the date of last clinical follow-up.

Recurrence-free survival (RFS) will be graphically displayed as Kaplan-Meier curves. Differences in survival times will be tested using a stratified (centre) log-rank test. The effect of treatment on time to failure will be estimated using a stratified (centre) proportional hazards regression model. Results will be presented as a hazard ratio (HR) together with a 90% confidence interval (CI), which corresponds to the one-sided hypothesis. As this is the

main endpoint in the study, a graph illustrating the estimated HR and 90% CI together with the non-inferiority margin (HR=1.57) will also be presented.

All analyses of RFS will be performed according to the intention-to-treat principle but may also be presented as per-protocol.

12.1.2 Secondary endpoints

Overall survival

Survival time will be calculated as the period between date of randomization to the date of death (any cause), or for patients still alive to the date of last clinical follow-up. Differences in survival times will be tested using a stratified log-rank test, and the effect of treatment on time to death will be estimated using a stratified proportional hazards regression model. Results will be presented as a hazard ratio (HR) together with a 90% confidence interval.

HRQoL

Data for the EORTC QLQ-C30/EN24 will be scored according to the algorithm described in the EORTC QLQ-C30 scoring manual .[80] All scales and single items are scored on categorical scales and linearly transformed to 0-100 scales where;

- a high score for a symptom scale or item represents a high level of symptoms or problems
- a high score for a functional scale represents a high or healthy level of functioning
- a high score for the global health status/QoL represents high QoL.

Compliance with completing the questionnaires will be investigated at each time point to evaluate the procedure for data collection and the feasibility of the questionnaires.

The effect of treatment, time, and the treatment-time interaction will be evaluated using linear mixed-models using all available longitudinal data on each of the scale scores at the different time points. Considering multiple testing, the results from the regression analysis will be presented as mean differences together with 99% confidence intervals.

In the interpretation of the EORTC QLQ-C30, CX-24 scores and the lymphoedema items a difference of ≥5 points on the 0–100 scales will be considered clinically important. Differences of 5–9 points are considered small, those of 10–20 as moderate, and ≥20 as large.[81] For EQ-5D published weights are available that allow for the creation of a single

summary score. Overall scores range from 0 to 1, with low scores representing a higher level of dysfunction and 1 as perfect health.

Intraoperative and Post-operative complications

Post-operative complications will be presented by numbers and percentages for each treatment. Differences in post-operative outcome will be tested using Fisher's exact test, but may also be presented as differences in proportions together with 99% confidence intervals to guard for multiple testing.

Diagnostic accuracy of the sentinel node biopsy

Assuming that 65% of participating women also participate in the sentinel node part of the trial and that 10% of participating women have lymph node metastases, at least 50 women with lymph node metastases will be recruited.

Under the null hypothesis that the sensitivity of the sentinel lymph node specimen is 85% and tested against a one-sided alternative with a desired sensitivity of at least 92.5% the study will be powered (with an alfa of 0.05 and beta 0.2) if ≥ 48 of the 50 women with lymph node metastases are correctly identified in their sentinel lymph node. Above according to first stage of the Fleming two stage design, which might be expanded to its second stage in the final analysis[82]. Exact 95% confidence intervals and sensitivity and negative predictive values are reported and estimated by proportions.

Health economics

Incremental cost-effectiveness ratio will be used to describe the differences between the two groups. If the two different study groups are equal in terms of oncological safety, estimations of both groups' costs, respectively, will be sufficient to judge which treatment is the most cost effective. However, if some of the study-arms shows a superior oncological safety, analytic models will be used. For health economic modeling a probabilistic sensitivity analysis will be included.

12.2 HYPOTHESIS

That RALS will not worsen RFS at 5 years by more than a maximum of 7.5%. Assuming a 5-year RFS of 85% for patients treated with standard treatment (radical hysterectomy and pelvic lymphadenectomy by laparotomy) this corresponds to a hazard rate of 1.57.

12.3 POWER CALCULATION

The clinical non-inferiority margin (NIM) is in this study defined as a 5-year RFS not worsened by more than 7.5%. To show that the 5-year RFS in the RALS arm is not worse than 77.5% compared to the expected 5-year rate of 85% in the standard arm, the study needs to observe 127 events with a one-sided level of significance (α) of 5% and a power (1-β) of 80%.

The NIM at 5-years correspond to a hazard ratio ($HR_{RALS\ vs\ Standard}$) of 1.57. If, at the time of the statistical analysis, the upper two-sided 90% confidence interval – this corresponds to a one-sided test at the 5% level – falls below 1.57, non-inferiority will be concluded.

12.4 SAMPLE SIZE

The third interim analysis (March 2025) by the DSMB was based on 35% of the necessary events (44/127), without any safety signals by randomization arm.

At the time of the third interim analysis, the observed event rate suggested a true 5-year RFS close to the initially assumed 85%, though the wide confidence intervals indicated that the true RFS could be higher. To ensure final study results would be available within 8 years of trial initiation—and to accommodate the possibility of a true 5-year RFS of 90%—the Trial Steering Committee decided in April 2025 to extend patient accrual to a maximum of 1,092 participants, if needed. This revised sample size was determined using the lower bound of the 95% confidence interval for the event rate at the time of the interim analysis. The extension (starting with patient 901) applies only to the primary endpoint, and the original power calculation remains unchanged.

The sample size ultimately depends on the true RFS in the RACC-trial. The following sensitivity analysis is an example of the changes in sample size depending on true RFS.

Standard RFS	**HR_{NIM}**	**Experimental RFS**	**Absolute NIM**	**Total events**	**Total sample size**
85%	1.568	77.5%	7.5%	127	768
87.5%	1.671	80.0%	7.5%	97	712
90%	1.826	82.5%	7.5%	72	656

12.5 INTERIM ANALYSIS AND STOPPING RULES

An independent safety and monitoring committee will review the data and carry out interim analyses according to 16.7. The first interim analysis is to be carried out 3 years after the first patient is randomized or when 300 patients have been included in the study, whichever comes first. The purpose of this interim analysis is to assess the overall failure (recurrence/death) rate, to assess the recruitment to the study and to make sure that none of the treatment groups appear to fare worse than the other. The committee may recommend terminating the study if a statistically significant ($p<0.001$) difference in RFS between the study groups is observed, or if the recruitment is so low that the necessary number of events is unlikely to be seen. The interim analysis is performed based on blinded data. If the committee determines that it is safe to proceed with the study, the results of the interim analysis will remain unknown to everyone except the committee members.

13 ETHICAL CONSIDERATIONS

13.1 RISK-BENEFIT CONSIDERATION

At present, two large studies have demonstrated that MIS is associated with a higher rate of recurrence and death from disease. This is clearly deeply concerning, especially since no clear cause has been established. Most industrialised countries have abandoned the open approach in favour of MIS with substantial investments in education and equipment. A return to open radical hysterectomy will dramatically affect the health care systems, especially in the Nordic countries. The centralisation of cancer care in the Nordic countries has been successful with effects on survival for several malignancies [83,84]. The use of nation-wide quality registers has further improved the oncologic management and constitutes a reliable data source for research and quality improvements. The preliminary analyses from the Danish and Swedish quality registers support previous retrospective data with no difference in DFS or OS between RALS and open surgery.

Since the LACC trial demonstrated an association between MIS and disease recurrence, the risk for similar outcomes in the RACC trial cannot be neglected. However, the potential risk should be balanced against the potential benefits including the preservation of an established surgical system, improved lymph node assessment, improved quality of life and future

developments within the robotic platform. An interim analysis will be performed as stated above.

This study will be conducted according to ICH-GCP, national law and guidelines and the Helsinki declaration. Before patient inclusion starts, this study protocol will be approved by an ethical review board in each country.

13.2 INSTITUTIONAL REVIEW BOARD/ETHICS COMMITTEE

The study protocol, patient information and informed consent form will be submitted to the ethics committee for approval. The study will only commence after approval by the ethics committee. All substantial protocol modifications must be submitted to the appropriate Independent Ethics Committee or Institutional Review Board for information and approval before implementation. Once approved by the appropriate Independent Ethics Committee or Institutional Review Board, the investigator shall implement such Protocol modifications. Protocol modifications for urgent safety matters shall however be directly implemented.

13.3 INFORMED CONSENT AND WITHDRAWAL

Before inclusion in the study, patients will be given oral and written information of the study aims, all treatment procedures and expected and possible adverse events. They will be informed as to the strict confidentiality of their patient data, and that their medical records will be reviewed by their treating physician and study personnel only. The patient is at any time, with or without given reason free to withdraw their consent to study participation, and this choice will not affect their subsequent treatment options or care.

Written Informed Consent must be obtained from all participants before enrolment in study. The Informed Consent Form should also be signed at the same occasion by the investigator who gave the written and verbal information. The Informed Consent Form should be filed in the Investigator´s File and one copy should be given to the study participant. The study participants will consent to: participate in the study; regulatory authorities and sponsor's representative (e.g. monitor) to gain full access to hospital records, to control the data collected in the study; recording, collecting and processing data and storing data in a database; and storing of study samples in a biobank (if the participating centre is part of the translational part of the RACC trial).

13.4 PATIENT PROTECTION AND GOOD CLINICAL PRACTICE

The responsible investigator will ensure that the study is conducted in agreement with the declaration of Helsinki and/or Swedish/National laws and regulations; whichever provides the greatest protection for the patient. The participant should be clearly informed that the data collected in the study will not identify any subject taking part in the study following the General Data Protection Regulation (GDPR) (EU 2016/679). Participating women will be treated according to the international guidelines on GCP as defined by the European Parliament (EG596/200).

13.5 SUBJECT IDENTIFICATION

Participating patients will be identified by a study specific code consisting of a two to six-digit number. This code will be used when registering the patient into the study database. The woman's national identification number will not be entered into the database. The key to the code will be available to the investigator only.

14 SIGNIFICANCE OF STUDY

The aim of the RACC trial is to establish the safety of robot-assisted radical hysterectomy for early-stage cervical cancer. Robot-assisted laparoscopy is currently the most common approach in the Nordic countries and it is of utmost importance to verify registry-based data in a prospective, randomized trial. In addition, the use of sentinel node biopsies is increasing although the accuracy and safety has not been established. The RACC trial has the potential to determine these aspects of the sentinel node concept.

15 ADMINISTRATIVE CONSIDERATIONS

15.1 FINANCING

This is an academic study sponsored by the coordinating investigator, Stockholm County Council, with no involvement of any external sponsor. The Clinical Trial Office at Center for Clinical Cancer studies, Theme Cancer, Karolinska University Hospital, Stockholm, Sweden will coordinate the study. All central administrative expenses related to the trial (statistics, monitoring, questionnaires) are covered by research grants.

The goal is to receive sufficient grants to partially or fully fund the study specific costs for each participating site. Each participating centre is free to seek financing of their own.

15.2 PUBLICATION POLICY

Before publication of the main oncological outcome, no other publication regarding oncological outcome on parts of the cohort can be attempted. The Coordinating investigator and study coordinator will be first and last author of the main oncologic outcome. The members of the trial steering committee must also be (co)-authors in all (other) publications. The members of each sub-committee will be authors of their respective sub-objective. The chair of each sub-committee will be first or last author and assembles the first draft of the manuscript. The coordinating investigator and study coordinator will be part of interpretation of data and order of authors for each publication from the sub-committees. One author (principal investigator) from each participating site, pending data completeness and quality, is to be co-author on any publication reporting on the main findings of the RACC trial, that is, any report on oncological outcome and other key publications. If number of authors are limited by the respective scientific journal, contributing sites that have recruited most participants and closed follow up will be selected. All investigators must agree to the fact that upon completion of data collection and analysis of data by study statistician, if the investigators are not in agreement with the outcomes of the results, they may elect to not be part of the authorship of the manuscript; however, the data entered from their site will be maintained and analysed as agreed at the initiation of the study and confirmed as per of this agreement.

15.2.1 Sub-analysis other than primary and secondary outcomes from the RACC trial

Further sub-analysis (other than the stated primary and secondary outcomes of the RACC trial) or other research projects from the participating investigators using data from RACC trial is allowed and encouraged but permission must be granted from the Trial Steering Committee after written application. The application must include; primary and secondary objective, inclusion/exclusion criteria, name of individual who will write the manuscript (including first and last author), intended name of journal for submission, and approval from respective institutional review board. The ultimate decision on authorship will be approved by the Trial Steering Committee.

15.3 ADHERENCE TO PROTOCOL AND PROTOCOL AMENDMENT

The study protocol must be adhered to. Any deviation must be documented and the Trial steering committee must be informed. Changes or supplements to the study protocol can only be decided on and authorized by the coordination investigator, study coordinator, trial

steering committee and statistician. Once approved by the appropriate Independent Ethics Committee or Institutional Review Board, the investigator shall implement such Protocol modifications. Protocol modifications for urgent safety matters shall however be directly implemented.

16 DATA MANAGEMENT AND QUALITY CONTROL

16.1 SOURCE DATA AND CASE REPORT FORM

Patient medical records will be source data and will be stored according to Good Clincial Practice (GCP) at, Karolinska Theme Cancer, Karolinska University Hospital. Data for this study will be recorded via an Electronic Data Capture (EDC) system, PheedIt, using an electronic Case Report Form (eCRF). It will be transcribed by the site from the paper source documents onto the eCRF. In no case is the eCRF to be considered as source data for this trial. Accurate and reliable data collection will be assured by verification and cross–check of the eCRFs against the investigator's records by the study monitor (source document verification).

The study database is situated in Sweden at the Center for Clinical Cancer studies, Theme Cancer at Karolinska University Hospital.

16.2 DATA RECORDING AND RECORD KEEPING

Data recording and data keeping will be managed by CTO, Center for Clinical Cancer studies, Theme Cancer, Karolinska University Hospital and stored for a minimum of 10 years after declaration of end of trial. All access to data via Principal Investigator or Investigators.

16.3 DATA PROTECTION

Recorded information is confidential and the database is privacy-protected; i.e., no data can be traced back to the patient in research reports and no unauthorized individuals may have access to the data about individuals in the database. The database will be maintained until further notice (at least 20 years after inclusion of the last patient) and be reported in accordance with the GDPR. The authority responsible for the database is Karolinska University Hospital, Stockholm, Sweden.

16.4 PARTICIPANT CONFIDENTIALITY

The investigator must assure that patients' anonymity will be maintained and that their identities are protected from unauthorized parties. On CRFs or other documents submitted to the Trial steering committee, patients should not be identified by their names, but by an identification code. The investigator should keep a patient enrolment log showing codes, names and addresses.

16.5 STORAGE OF STUDY DOCUMENTS

To comply with national and international guidelines patient´s identification list and patient records and other study related documents will be retained for at least 10 years after the closure of the trial. This data will only be available to investigator(s) and investigator appointed personnel involved in the clinical trial.

16.6 QUALITY CONTROL AND MONITORING

The quality control of this trial in Sweden will be performed by CTO, Center for Clinical Cancer studies, Theme Cancer, Karolinska University Hospital.

This trial will be monitored regularly according to GCP and local regulations. All information reported in the eCRFs will also be documented in the patient´s file unless otherwise specified. The investigator will allocate adequate time for visits performed by the monitor. The investigator will also ensure that the monitor is given access to source documents which support data entered into the eCRF´s. The investigator further assures direct access to source data for possible trial-regulated regulatory audits.

16.7 DATA SAFETY MONITORING BOARD (DSMB) AND INTERIM ANALYSES

An independent Data Safety Monitoring Board (DSMB) will be appointed by the Trial Steering Committee. The aim of the DSMB is to safeguard the interest of trial participants and to ensure adequate accrual rate. The DSMB will be blinded to the treatment allocation. The DSMB will carry out interim analyses during the trial according to the following time points and objectives:

1. Assesment of accrual rate at 3 years after trial launch. The purpose is to ensure adequate accrual rate for completing the inclusion period of the trial within 5 years.
2. Assessment of primary endpoint events (recurrence/death) at 700 enrolled patients. The purpose is to analyse the event rate and conduct a conditional power analysis based on the number of events at that time point.

3. Assesment of primary endpoint events (recurrence/death). The analyses will be performed after every 30 documented events (i.e. after 30, 60, 90, 120 events).

After each interim analysis, the DSMB will make one of the following recommendations:

1. No actions needed; the trial contiunes as planned
2. Temporarily stop accrual, awaiting further inquiry and observation
3. Early termination due to clear harm of any of the allocated treatment arms or futility or external evidence.
4. Extend accrual based on the results of the conditional power analysis.

In addition, the DSMB may also recommend to alter the statistical plan if the true RFS appears significantly higher or lower than expected as this will affect the required number of events (see 11.4). The advice(s) of the DSMB will only be sent to the Trial Steering Committee of the study. Further details of the DSMB are outlined in the charter DSMB (Appendix 17.12).

17 APPENDICES

17.1 FIGO

FIGO staging cervical cancer [13]

Stage I:

The carcinoma is strictly confined to the cervix uteri (extension to the corpus should be disregarded)

- **IA** Invasive carcinoma that can be diagnosed only by microscopy, with maximum depth of invasion <5 mm[a]
  - **IA1** Measured stromal invasion <3 mm in depth
  - **IA2** Measured stromal invasion ≥3 mm and <5 mm in depth
- **IB** Invasive carcinoma with measured deepest invasion ≥5 mm (greater than stage IA), lesion limited to the cervix uteri[b]
  - **IB1** Invasive carcinoma ≥5 mm depth of stromal invasion and <2 cm in greatest dimension
  - **IB2** Invasive carcinoma ≥2 cm and <4 cm in greatest dimension
  - **IB3** Invasive carcinoma ≥4 cm in greatest dimension

Stage II:

The carcinoma invades beyond the uterus, but has not extended onto the lower third of the vagina or to the pelvic wall

- **IIA** Involvement limited to the upper two-thirds of the vagina without parametrial involvement
  - **IIA1** Invasive carcinoma <4 cm in greatest dimension
  - **IIA2** Invasive carcinoma ≥4 cm in greatest dimension
- **IIB** With parametrial involvement but not up to the pelvic wall

Stage III:

The carcinoma involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or non-functioning kidney and/or involves pelvic and/or paraaortic lymph nodes[c]

- **IIIA** Carcinoma involves the lower third of the vagina, with no extension to the pelvic wall
- **IIIB** Extension to the pelvic wall and/or hydronephrosis or non-functioning kidney (unless known to be due to another cause)
- **IIIC** Involvement of pelvic and/or paraaortic lymph nodes, irrespective of tumor size and extent (with r and p notations)[c]
  - **IIIC1** Pelvic lymph node metastasis only
  - **IIIC2** Paraaortic lymph node metastasis

Stage IV:

The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. A bullous edema, as such, does not permit a case to be allotted to stage IV

- **IVA** Spread of the growth to adjacent organs
- **IVB** Spread to distant organs

[a]Imaging and pathology can be used, when available, to supplement clinical findings with respect to tumor size and extent, in all stages.

[b]The involvement of vascular/lymphatic spaces does not change the staging. The lateral extent of the lesion is no longer considered.

[c]Adding notation of r (imaging) and p (pathology) to indicate the findings that are used to allocate the case to stage IIIC. For example, if imaging indicates pelvic lymph node metastasis, the stage allocation would be stage IIIC1r and, if confirmed by pathological findings, it would be Stage IIIc1p. The type of imaging modality or pathology technique used should always be documented. When in doubt, the lower staging should be assigned.

17.2 CLAVIEN

Postoperative complications within 30 days after surgery according to Clavien Dindo [85]

APPENDIX A. Classification of Surgical Complications

Grades	Definition
Grade I:	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions.
	Acceptable 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 transfusions and total parenteral nutrition are also included.
Grade III:	Requiring surgical, endoscopic or radiological intervention
Grade III-a:	intervention not under general anesthesia
Grade III-b:	intervention under general anesthesia
Grade IV:	Life-threatening complication (including CNS complications)‡ requiring IC/ICU-management
Grade IV-a:	single organ dysfunction (including dialysis)
Grade IV-b:	multi organ dysfunction
Grade V:	Death of a patient
Suffix 'd':	If the patient suffers from a complication at the time of discharge (see examples in Appendix B, http://Links.Lww-.com/SLA/A3), the suffix "d" (for 'disability') is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.

‡ brain hemorrhage, ischemic stroke, subarrachnoidal bleeding, but excluding transient ischemic attacks (TIA); IC: Intermediate care; ICU: Intensive care unit
www.surgicalcomplication.info

17.3 CTCAE 3.0

Lymphatic side effects according to the Common Terminology Criteria (CTC) version 3.0 [86]

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4
Lower extremity lymphedema	5%–10% inter-limb discrepancy in volume or circumference at point of greatest visible difference; pitting edema	10–30% inter-limb discrepancy in volume or circumference at point of greatest visible difference	>30% inter-limb discrepancy in volume; lymphorrhea, interfering with activities of daily life	Progression to malignancy (i.e. lymphangiosarcoma), amputation indicated, disabling
Truncal/genital lymphedema	Swelling or obscuration of anatomic architecture on close inspection, pitting edema	Readily apparent obscuration of anatomic architecture; obliteration of skin folds	Lymphorrhea; interfering with activities of daily life; gross deviation from normal anatomical contour	Progression to malignancy (i.e. lymphangiosarcoma); disabling
Lymphocele	Asymptomatic, clinical or radiographic findings only	Symptomatic; medical intervention indicated	Symptomatic and interventional radiology or operative intervention indicated	–

17.4 INTRAOPERATIVE ADVERSE EVENTS

According to Rosenthal et al [87].

Table 2 Proposed *Class*ification of *I*ntraoperative *C*omplications (CLASSIC)

Grade	Definition
	The classification exclusively relates to any event occurring between skin incision and skin closure and should be rated directly after surgery. Any event during the index-surgery must be considered, regardless whether it is surgery or anesthesia-related[a].
	Prerequisite: the indication for surgery and the interventions conform to current guidelines
Grade 0	No deviation from the ideal intraoperative course
Grade I	Any deviation from the ideal intraoperative course
	• Without the need for any additional treatment or intervention
Grade II	Any deviation from the ideal intraoperative course
	• With the need for any additional treatment or intervention
	• Not life-threatening and not leading to permanent disability
Grade III	Any deviation from the ideal intraoperative course
	• With the need for any additional treatment or intervention
	• Life-threatening and/or leading to permanent disability
Grade IV	Any deviation from the ideal intraoperative course
	• With death of the patient

[a] The following events are not defined as intraoperative complications: sequelae, failures of cure, events related to the underlying disease, wrong-site or wrong-patient surgery, or errors in indication

According to Kaafarani et al [88].

Table 1. Intraoperative Adverse Event Severity Classification Scheme

Class	Description
I	Injury requiring no repair within the same procedure (eg, cauterization, use of prothrombotic material, small vessel ligation)
II	Injury requiring surgical repair, without organ removal or a change in the originally planned procedure (eg, any suture repair, patch repair)
III	Injury requiring tissue or organ removal with completion of the originally planned procedure
IV	Injury requiring a significant change* and/or incompletion of the originally planned procedure
V	Missed intraoperative injury requiring re-operation within 7 days
VI	Intraoperative death
Suffix T	Add if injury required transfusion of ≥2 U blood

*Excludes minimally invasive to open conversions.

Table 2. Generic Examples of Intraoperative Adverse Events at Each Severity Class

Severity class	Intraoperative adverse event examples
I	Small blood vessel tear followed by ligation of the vessel Small liver laceration repaired with electrocautery and Surgicel (Ethicon)
II	Small enterotomy repaired primarily Cystotomy repaired primarily in 2-layer closure
III	Enterotomy requiring small bowel resection Splenic injury requiring splenectomy
IV	Common bile duct injury during cholecystectomy necessitating a hepaticojejunostomy A hepatic artery injury necessitating repair of the defect using a bypass graft
V	A missed iatrogenic splenic injury requiring reoperation 24 to 48 hours postoperatively for bleeding A missed iatrogenic enterotomy requiring reoperation 4 days postoperatively
VI	Intraoperative death due to uncontrolled hemorrhage

17.5 OPERATIVE REPORT INCLUDING LABELLING OF LYMPH NODE SPECIMENS AND LOCATION OF SENTINEL LYMPH NODES

Version 1.0

RACC-TRIAL OPERATIVE REPORT

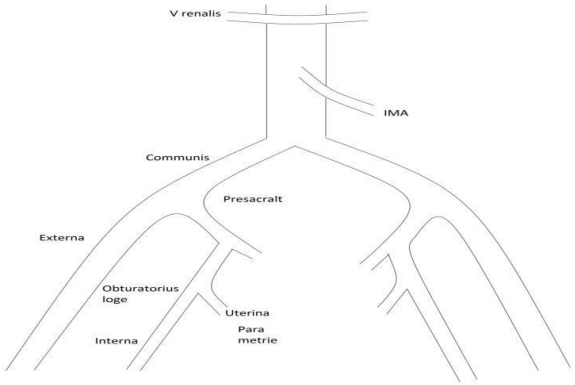
Participant ID:_____

Hospital/Institution:	**City:**	**Country:**
Date of surgery (ddmmyyyy):	**Surgical approach according to randomisation**	Yes No
Surgical approach	Robot-assisted laparoscopic	Laparotomy
Operation time skin to skin: minutes	**OR time Patient in Patient out:** minutes	**Estimated blood loss:** mL
Type of radical hysterectomy according to Querleu-Morrow classification	B1 B2 C1	
Vaginal closure before colpotomy (any method)	Yes	No
Salpingectomy	Yes	No
Oophorectomy	Yes	No
Transposition of ovaries	Yes	No
Nerve sparing surgery	Yes	No
Converted from Robotic to Open surgery	Yes	No
If Yes, select indication(s)	Bleeding Surgical complexity/adhesions	Macroscopic dissemination of disease in the abdomen Specify: Lymph node Parametrium Other: _____
Any intraoperative complications	Yes No	
If yes, specify:	Severity (grade) according to **Rosenthal et al.**	Severity (class) according to **Kaafarani et al.**
Urinary bladder	____	____
Ureter	____	____
Small Bowel	____	____
Colon	____	____
Small bowel	____	____
Blood Vessel	____	____
Abdominal wall	____	____
_____	____	____
_____	____	____
_____	____	____

RACC-TRIAL OPERATIVE REPORT

Participant ID:_____

Part of the sentinel lymph node sub-study ☐Yes ☐No	**If yes, other than RACC-trial protocol** ☐Yes ☐No	**If yes, specify method:**_____
Other Sentinel lymph node algorithm than RACC-trial algorithm ☐ Unilateral pelvic mapping ☐ Bilateral pelvic mapping	In case of uni or bilateral non-mapping, has sampling been performed according to the trial protocol ***(mandatory):*** ☐Yes ☐No	
RACC-protocol Sentinel lymph node mapping ☐Yes ☐No If yes, display after first injection: UPP Right after first injection ☐Yes ☐No UPP Left after first injection ☐Yes ☐No LPP Right after first injection ☐Yes ☐No LPP Left after first injection ☐Yes ☐No	**Reinjection of ICG in the Uterine cervix**: ☐Yes ☐No If yes, display after reinjection: UPP Right after reinjection ☐Yes ☐No UPP Left after reinjection ☐Yes ☐No LPP Right after reinjection ☐Yes ☐No LPP Left after reinjection ☐Yes ☐No	
Localisation of SLN UPP Right: ☐External iliacs ☐Obturator ☐ Common iliacs	**Type of SLN UPP Right:** ☐Type 1 ☐Type 2 ☐Macro ☐Sampling	
Localisation of SLN UPP Left: ☐External iliacs ☐Obturator ☐ Common iliacs	**Type of SLN UPP Left:** ☐Type 1 ☐Type 2 ☐Macro ☐Sampling	
Localisation of SLN LPP Right: ☐Iliaca interna medial side ☐Presacral ☐ Paraaortic below IMA	**Type of SLN LPP Right:** ☐Type 1 ☐Type 2 ☐Macro ☐Sampling	
Localisation of SLN LPP Left: ☐Iliaca interna medial side ☐Presacral ☐ Paraaortic below IMA	**Type of SLN LPP Left:** ☐Type 1 ☐Type 2 ☐Macro ☐Sampling	
Extra-pelvic ICG positive lymph node without ICG positive lymph node in the pelvis: ☐Yes ☐No	**ICG uptake in IP ligament:** ☐Yes ☐No	



Instructions: Only one marking for each Sentinel lymph node with jar number and type of SLN, see below.

○ = **SLN type 1** (ICG positive sentinel node)

□ = **SLN type 2 (**ICG negative node with obvious afferent ICG positive lymphatic vessel adjacent to the uterus)

X = **SLN macro (**By the naked eye lymph node suspicious of metastasis with or without uptake of ICG)

Δ = **SLN-sampling** (non-display of ICG, mapping failure, see Figure 3 for exact anatomic locations to sample)

Date (ddmmyyyy) of completion of this operative report:

Operative report filled by Dr:

Labeling of lymph node specimens RACC trial Participant ID:

Number	Lymph node basin/station	Number to pathologist*
1	LN External iliacs Right side	
2	LN Obturator fossa Right side	
3	LN Common iliacs Right side	
4	LN Presacral Right side	
5	LN External iliacs Left side	
6	LN Obturator fossa Left side	
7	LN Common iliacs Left side	
8	LN Presacral Left side	
(9)	LN Paraaortic below the IMA	
(10)	LN Paraaortic above the IMA	
11	SLN type 1	
12	SLN type 1	
13	SLN type 1	
14	SLN type 1	
15	SLN type 1	
16	SLN type 1	
17	SLN type 2	
18	SLN type 2	
19	SLN type 2	
20	SLN macro	
21	SLN macro	
22	SLN sampling	
23	SLN sampling	
24	SLN sampling	
25	SLN sampling	
26	SLN sampling	
27	SLN sampling	
28	SLN sampling	
29	SLN sampling	
30		
31		
32		
33		
34		

If a lymph node (LN) specimen from a station is missing the row is deleted but the number for each station remains. The position of the Sentinel Lymph Nodes (SLNs) are written by the surgeon during surgery and anatomic position of the SLN and type of SLN is also marked in the illustration. Each number have a corresponding sticker which is labelled on the jar for histopathological review. The stickers for SLNs are red. It is helpful to also write to location of SLN in the above chart by hand. Number 30-34 are for eventual circumstances and the sticker must then be written and labelled by hand. *According to local guidelines if applicable.

3/3

RACC-TRIAL OPERATIVE REPORT

Participant ID:_____

Version 1.0

Positions of SLN in cervical cancer following cervical injection of ICG

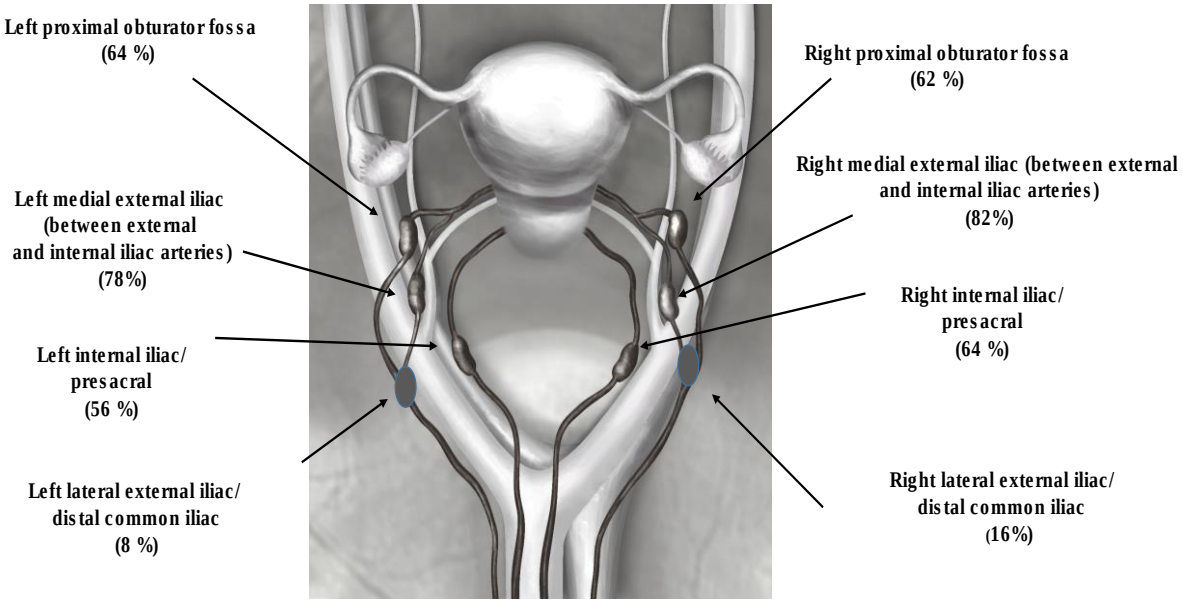


Figure 3

17.6 ICG DILUTION, DOSE AND INJECTION

Indocyanine Green solution (ICG)	**2.5mg/mL**
Manufacturer	Pulsion medical system, Feldkirchen Germany
Availability	ICG will be provided by the manufacturer to each site.
Description	Is a sterile, lyophilized green powder containing 25 mg of Indocyanine green with no more than 5% sodium iodide.
Preparation	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. 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.
Injection site	Half the ICG volume in each of four syringes is injected in the cervical sub-mucosa 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. The display of ICG in the respective pathways will be evaluated a minimum 10 minutes after the injection of ICG A second ipsilateral injection of 0,25mL ICG is performed in case of non-display of either of lymphatic 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 in the cervical sub-mucosa and half the volume 3 cm into the cervix.
Storage	The ICG solution is stored at room temperature. The solution is active for 6 hours, and should be discarded after that period of time.

17.7 SITE IDENTIFICATION AND QUALITY ASSESSMENT FORM

Robot-assisted Approach to Cervical Cancer

Robot-assisted surgery versus laparotomy in women with early cervical cancer

Dear Investigator,

Thank you for being interested in participating in the RACC trial.

In order to evaluate the feasibility of your site for participation some information regarding surgical quality and resources needs to be disclosed.

Please read, complete and sign the following documents together with the required reports and send it by email to: *sahar.salehi@sll.se*

According to the study protocol the following criteria are to be fulfilled by centers considered for participation in the trial.

- Established robotic surgery unit for at least 3 years
- At least 10 radical hysterectomies for early stage cervical cancer per year in the unit
- Minimum of 20 radical upfront debulking surgeries per year for advanced ovarian cancer
- Intensive care unit available
- Ability to perform ultrastaging of lymph nodes
- Ability to review all specimens by a reference pathologist

The Trial Steering Committee requires following information from each institution before initiation, data is required for the last 24 months:

- 10 anonymized surgical reports of patients that have undergone radical hysterectomy for cervical cancer
- 10 anonymized surgical reports of patients operated upfront with radical debulking surgery for advanced ovarian cancer
- For each patient, the surgical report is accompanied by corresponding anonymized pathological report.
- Attached to each surgical report, operation time in minutes, per-operative bleeding in mL and 30-day postoperative complications according to Clavien Dindo classification must be stated.

Robot-assisted Approach to Cervical Cancer

Robot-assisted surgery versus laparotomy in women with early cervical cancer

Information on study site

Hospital name	
Department	
Street	
Zip code/City/Country	
Principal investigator	
Participating surgeons	
Research coordinators and study nurses/assistants	
Telephone number **Investigator** **Research Coordinator**	
Fax **Investigator** **Research Coordinator**	
Email **Investigator** **Research Coordinator**	

Robot-assisted Approach to Cervical Cancer

Robot-assisted surgery versus laparotomy in women with early cervical cancer

Facilities/Technique/Resources

Centralized care of cervical cancer patients	☐ yes	☐ no
Intensive Care unit available	☐ yes	☐ no
Access to transfusions	☐ yes	☐ no
Access to medical and radiation oncology	☐ yes	☐ no
Capacity to perform surgery within 4 weeks of enrollment	☐ yes	☐ no
Close documentation within 4 weeks after each planned visit according to protocol can be assured	☐ yes	☐ no

Specify available resources for documentation:

Name of responsible person for documentation:

Agreement to use an e-CRF	☐ yes	☐ no
Agreement to register all patients eligible with early stage cervical cancer into a screening log	☐ yes	☐ no
Agreement to be visited and audited by RACC Trial Steering committee members during the recruitment period of the study	☐ yes	☐ no

Robot-assisted Approach to Cervical Cancer

Robot-assisted surgery versus laparotomy in women with early cervical cancer

Surgery and histopathology

Radical Hysterectomies with lymph node dissection _____ per year

Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer patients with upfront surgery _____ per year

Radical hysterectomy with lymph node dissection

Year 2017: _____ pts operated,
_____ pts with sentinel node biopsy
Proportion of operations in robot ≈_____ %

Year 2018: _____ pts operated,
_____ pts with sentinel node biopsy
Proportion of operations in robot ≈_____ %

Radical Upfront Debulking Surgery in FIGO Stage III-IV Ovarian or fallopian tube cancer patients

Year 2017: _____ pts operated,
_____ complete resections,
Proportion of complete tumor resection achieved ≈_____ %

Year 2018: _____ pts operated,
_____ complete resections,
Proportion of complete tumor resection achieved ≈_____ %

Ability to perform ultrastaging of lymph nodes and possibly many lymph nodes ☐ yes ☐ no

Access to a gynaecologic reference pathologist ☐ yes ☐ no

Ability to close documentation on pathology report within 6 weeks after surgery ☐ yes ☐ no

Robot-assisted Approach to Cervical Cancer

Robot-assisted surgery versus laparotomy in women with early cervical cancer

Interest in participating in the sentinel node part of the RACC trial	☐ yes	☐ no
If yes, interested in adherence to the RACC-trial protocol (see protocol 5.4) and accepting on-site training from the Trial steering committee	☐ yes	☐ no
If yes, interested but with other/own algorithm	☐ yes	☐ no
If yes, please provide detailed description of your algorithm on a separate document and attach to the Site Quality Assessment Form		

Adjuvant Treatment

Standard adjuvant treatment for patients fulfilling critera after primary surgery for early stage Cervical cancer is Extern radiotherapy, standard dose 45 Gy with weekly Cisplatin 40 mg/m^2	☐ yes	☐ no
If no, please specify in a separate word document the standard adjuvant treatment		
Do you use Sedlis critera to select patients for adjuvant treatment?	☐ yes	☐ no
If no, please specify in a separate word document how you select patients actual for adjuvant treatment and attach the document.		
Please provide details on the proportion of operated patients with early stage cervical cancer subjected to adjuvant treatment during the last 24 months.	_____%	

Robot-assisted Approach to Cervical Cancer

Robot-assisted surgery versus laparotomy in women with early cervical cancer

The principal investigator of each centre is responsible that all the above criteria are met by the operating team and can assure that all required information is available and emailed after scanning as PDF to the study group at the following address:

sahar.salehi@sll.se

Registration of your information in the Site identification and quality assessment form of the RACC trial will result in Karolinska University Hospital processing your personal data. Acceptance is a prerequisite and your signature below a confirmation of acceptance. For more information about personal data, contact the data protection officer *(Dataskyddsombud.karolinska@sll.se).*

Date and Signature of Prinicpal Investigator

Thank you very much for your interest in this study!

17.8 EORTC QLQ-C30

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊_⌋⌊_⌋⌊_⌋⌊_⌋

Your birthdate (Day, Month, Year): ⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋

Today's date (Day, Month, Year): 31 ⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

17.9 QLQ-CX24

EORTC QLQ – CX24

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems, please answer by circling the number that best applies to you.

During the past week:		**Not at all**	**A little**	**Quite a bit**	**Very much**
31.	Have you had cramps in your abdomen?	1	2	3	4
32.	Have you had difficulty in controlling your bowels?	1	2	3	4
33.	Have you had blood in your stools (motions)?	1	2	3	4
34.	Did you pass water/urine frequently?	1	2	3	4
35.	Have you had pain or a burning feeling when passing water/urinating?	1	2	3	4
36.	Have you had leaking of urine?	1	2	3	4
37.	Have you had difficulty emptying your bladder?	1	2	3	4
38.	Have you had swelling in one or both legs?	1	2	3	4
39.	Have you had pain in your lower back?	1	2	3	4
40.	Have you had tingling or numbness in your hands or feet?	1	2	3	4
41.	Have you had irritation or soreness in your vagina or vulva?	1	2	3	4
42.	Have you had discharge from your vagina?	1	2	3	4
43.	Have you had abnormal bleeding from your vagina?	1	2	3	4
44.	Have you had hot flushes and/or sweats?	1	2	3	4
45.	Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
46.	Have you felt less feminine as a result of your disease or treatment?	1	2	3	4
47.	Have you felt dissatisfied with your body?	1	2	3	4

Please go on to the next page

During the past 4 weeks:		**Not at all**	**A little**	**Quite a bit**	**Very much**
48.	Have you worried that sex would be painful?	1	2	3	4
49.	Have you been sexually active?	1	2	3	4

Answer these questions only if you have been sexually active during the past 4 weeks:		**Not at all**	**A little**	**Quite a bit**	**Very much**
50.	Has your vagina felt dry during sexual activity?	1	2	3	4
51.	Has your vagina felt short?	1	2	3	4
52.	Has your vagina felt tight?	1	2	3	4
53.	Have you had pain during sexual intercourse or other sexual activity?	1	2	3	4
54.	Was sexual activity enjoyable for you?	1	2	3	4

17.10 LYMQOL[76]

Lymphoedema Quality of Life Study (LYMQOL) LEG

If any of the items are not applicable to you, please write N/A in the relevant answer box(es).

(1) Has your swollen leg(s) affected:				
	Not at all	A little	Quite a bit	A lot
a) your walking				
b) your ability to go up and down stairs				
c) your ability to bend, e.g. to tie shoelaces or cut toenails				
d) your ability to kneel				
e) your ability to stand				
f) your ability to get into/out of a car				
g) Your ability to get on/of public transport, e.g. trains/buses				
h) your ability to get up from a chair				
i) your ability to drive a car				
j) your occupation				
k) your ability to do housework				
(2) Does the swelling affect your leisure activities/social life?				

Please give example(s) of this.

(3) How much do you have to depend on other people?				
(4) How much do you feel the swelling affects your appearance?				
(5) How much difficulty do you have finding clothes to fit?				
(6) How much difficulty do you have finding clothes you would like to wear?				
(7) Do you have difficulty finding shoes to fit?				
(8) Do you have difficulty finding socks/tights/stockings to fit?				
(9) Does the swelling affect how you feel about yourself?				
(10) Does it affect your relationship with your partner?				
(11) Does it affect your relationships with other people?				
(12) Does your lymphoedema cause you pain?				
If so, do you have pain in the foot/feet				
leg/legs				
hip(s)				
back				
elsewhere — if so, where?				
(13) Do you have any numbness in your swollen leg(s)?				
(14) Do you have any feelings of 'pins and needles' or tingling in your swollen leg(s)				
(15) Does (do) your swollen leg(s) feel weak?				
(16) Does (do) your swollen leg(s) feel heavy?				
(17) Does (do) your swollen foot (feet) feel 'old'?				
(18) Have you had any leakage of fluid from your leg(s)				
In the past week				
(19) Have you had trouble sleeping?				
(20) Have you had difficulty concentrating on things, e.g. reading?				
(21) Have you felt tense?				
(22) Have you felt worried?				
(23) Have you felt irritable?				
(24) Have you felt depressed?				

(25) Overall, how would you rate your quality of life at present? Please mark your score on the following scale:

Poor	0	1	2	3	4	5	6	7	8	9	10	Excellent

Thank you for completing this form.

If you have any comments or queries about it, please discuss these with..... Dr V L Keeley, Consultant

Questions 19 to 25 have been reproduced with permission from the EORTC. These questions are only a part of the QLQ-C30 Questionnaire.

17.11 EQ5D-3L

By placing a tick in one box in each group below, please indicate which statemer describe your own health state today.

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

Usual Activities *(e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain / Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety / Depression

I am not anxious or depressed ❑

I am moderately anxious or depressed ❑

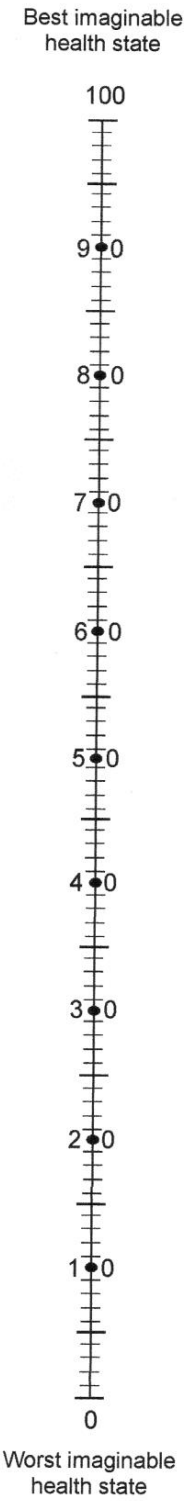
I am extremely anxious or depressed ❑

2

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



3

17.12 DATA SAFETY AND MONITORING CHARTER

1. Introduction	
Name of trial	RACC-trial (Robot Assisted approach to Cervical Cancer)
Study risk classification	Medium
Objectives of trial, including	The RACC trial is an international multicenter randomized study.
Interventions being investigated	Interventions being investigated comparing outcomes of robot assisted laparoscopic radical hysterectomy and abdominal radical hysterectomy for cervical cancer. The study will include a quality assessment phase before randomization to ensure required competency level of participating centers and surgeons. During the trial the clinical data will be reviewed centrally to ensure uniform quality. The primary endpoint of the RACC trial is recurrence-free survival (RFS) at 5 years. Secondary endpoints include overall survival, morbidity, diagnostic accuracy of sentinel node biopsy, health care costs and quality of life.
Outline of scope of charter	The purpose of this document is to describe the roles and responsibilities of the independent Data Safety and Monitoring Board (DSMB) for the RACC trial, including the timing of meetings, methods of providing information to and from the DSMB, frequency and format of meetings, statistical issues and relationships with other committees
2. Roles and responsibilities	

A broad statement of the aims of the committee	To safeguard the interests of trial participants and assess the safety of any of the randomized allocated treatment arms during the trial
Terms of reference	The DSMB should receive and review the safety data of this trial. The DSMB should inform the Trial Steering Committee (TSC) if, in their view: ○ Slow trial accrual at 3 years after trial launch. The DSMB may, at this point, recommend to terminate the trial for futility ○ The inclusion should be extended based on a conditional power analysis at 700 included patients ○ Interim review for every 30 documented events in the Trial
Specific roles of DSMB	The DSMB will be supplied with all relevant data at the above-mentioned time points to evaluate the inclusion rate and unexpected differences in primary endpoint between the study arms (blinded to treatment allocation) and potential conflicts with new insights and/or developments within the field of cervical cancer. It is at the discretion of the DSMB to meet early in the course of the trial and to discuss the protocol including the interim analysis plan, and to have the opportunity to clarify any aspects with the Coordinating investigator/Sponsor
3. Composition	
Membership and size of the DSMB	DSMB members register their assent by confirming (1) that they agree to be on the DSMB and (2) that they agree with the contents of this Charter. The members are independent of the Trial and have no competing interests that could impact on the Trial. The members of the DSMB for this trial are:

	(1) *Professor Mats Brännström, Chair (Gynecologic oncologist surgeon, Sahlgrenska Academy, Gothenburg, Sweden)* (2) *Professor Elisabeth Åvall-Lundqvist (Chair; Gynecologic medical oncologist, Linköpings University Hospital, Linköping, Sweden)* (3) *PhD Erik Holmberg (Statistician, Regional Cancer Center, Gothenburg, Sweden)* The Trial Coordinating Investigator may be asked, and will be available to attend open sessions of the DSMB meeting. The other TSC members will not usually be expected to attend but can attend when necessary
4. Relationships	
Clarification of DSMB role	No payments or rewards will be awarded to the DSMB.
Competing interests	Competing interests of DSMB members – financial matters, involvement in other trials or intellectual investment should be disclosed. DSMB members should not use interim results to inform trading in pharmaceutical shares, and careful consideration should be given to trading in stock of companies with competing products.
5. Organization of DSMB meetings	
Expected frequency of DSMB meetings	The DSMB will meet at least once in the first year after the start of participant inclusion. The DSMB will perform interim analyses as mentioned above (2. Roles and responsibilities, Terms of reference). The meetings of the DSMB can be by conference call, as long as full discussion with all members can be guaranteed. All sessions are in principle open, although the DSMB can decide otherwise
6. Trial documentation and procedures to ensure confidentiality and proper communication	
Intended content of material to be available in open sessions	Accumulated information relating to the trial's safety data will be presented. Other outcome measures (e.g. accrual rate) may be presented, at the discretion of the DSMB.

	The DSMB members will be blinded to the treatment allocation.
Who will see the accumulating data and interim analysis	The DSMB will discuss the results of the interim analysis with the TSC. DSMB members do not have the right to share confidential information with anyone outside the DSMB, other than the TSC.
External evidence	The Coordinating Investigator/Sponsor will identify and circulate external evidence that can influence the trial.
To whom the DSMB will communicate the decisions/ recommendations that are reached	The DSMB reports its recommendations in writing to the TSC. The DSMB members should store the documents safely after each meeting so they may check the next report against them. After the trial is reported, the DSMB members should destroy all interim reports.
7. Decision making	
Decisions/recommendations open to the DSMB	Possible recommendations: • No action needed; trial continues as planned • Temporarily stop accrual, awaiting further inquiry and observation • Early stopping due, for example, to clear harm of any of the allocated treatment arms, futility, or external evidence • Extend accrual based on the conditional power analysis at 700 enrolled patients
Decisions or recommendations within the DSMB	Every effort should be made for the DSMB to reach a unanimous decision. If the DSMB cannot achieve this, a vote may be taken, although details of the vote should not be routinely included in the report to the TSC as these may inappropriately convey information about the state of the trial data.

	It is important that the implications (e.g. ethical,statistical, practical, and financial) for the trial be considered before any recommendation is made. Effort should be made for all members to attend DSMB meetings. Chair will try to ensure that a date is chosen to enable this. If a member does not attend a meeting, it should be ensured that the member is available for the next meeting. If a member does not attend a second meeting, they should be asked if they wish to remain part of the DSMB. If a member does not attend a third meeting, they should be replaced and the Trial Coordinating Investigator be notified.
8. Reporting	
Recommendations/decisions of the DSMB **Disagreement between the DSMB and TSC**	The DSMB will report their recommendations/decisions in a letter to the TSC, within 4 weeks after the meeting If the DSMB has serious problems or concerns with the TSC decision based on the report, a meeting of these groups should be held. The information to be shown would depend upon the action proposed and the DSMB's concerns. Depending on the reason for the disagreement confidential data (still blinded) will have to be revealed to all those attending such a meeting. The meeting will be chaired by an external expert who is not directly involved with the trial.
9. After the trial	
Publication of results	If requested by the DSMB, a meeting at the end of the trial will be held to allow the DSMB to discuss the final data with the principal trial investigators and give advice about data interpretation. The DSMB will be given the opportunity to read and comment on any publication before submission, especially with respect to reporting of any DSMB recommendation regarding termination of a trial.

	The DSMB may discuss issues from their involvement in the trial when permission is agreed with the overseeing committee.

17.13 A RADIOMICS EXPANSION OF THE RACC TRIAL STUDY – ID_ MAORI

Original protocol: The RACC trial –Robot-assisted Approach to Cervical Cancer

A radioMics expAnsiOn of the RACC tRIal study – ID_ MAORI

Clinical coordinating center: Theme Cancer, Karolinska University Hospital, Stockholm, Sweden
RACC trial coordinating investigator: Henrik Falconer, Theme Cancer, Karolinska University Hospital, Stockholm, Sweden
Radiomics coordinating centers: Fondazione Policlinico Universitario "A. Gemelli" IRCCS, Rome, Italy

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1. Background and rationale: radiomics as an emerging field for precision medicine

Radiomics is a high-throughput approach to translate medical images into minable data by extracting a large number of quantitative features describing tumor intensity, shape and texture.
We hypothesize that radiomics features, being a robust quantification of imaging phenotypes, will potentially add layer in early and accurate radiogenomics diagnosis, prognostication and treatment stratification in cervical cancer. Tumor heterogeneity shows significant correlations with radiomics in a variety of cancer patients, including cervical cancer [1-5].
Some preliminary experiences on cervical cancer pretreatment imaging to characterize cervical lesions, predict local response and assess tumor biological heterogeneity have already been reported [6-9].
Besides imaging studies, large-scale molecular profiling using next-generation sequencing platforms has provided comprehensive insights into tumor genomics but it requires tissue extraction, which is frequently limited by its invasiveness and costs while, on the other hand, imaging is routinely used for diagnosis, tumour staging, treatment planning, and surveillance with the advantage to be less invasive and expensive.
The recent advances in radiomics data processing and analyses have allowed in-depth and quantitative, not invasive, readily accessible tumor characterisation as a whole, including intratumoral heterogeneity that may enhance predictive models' performances using standard staging imaging (MRI and ^{18}FDG-PET-CT).
Primary aims of this study additional to the RACC protocol is the development of a radiomics model for the prediction of Recurrence free survival (RFS) of the enrolled patients for the primary study considered timeframe of 8 years (inclusion 5 years and follow-up 3 years).

Secondary aims of this study are:

- Development of a radiomics models for the prediction of HPV mutational status (using ctDNA)
- Development of a radiomics model for the prediction of overall survival (OS)
- Development of a radiomics model to describe tumor heterogeneity using histological subgroups as ground truth
- Development of clinical decision support systems (DSS) and predictive models.

2. Patients cohorts and available image datasets

The same patient-cohort of the primary RACC trial study will be used for these investigations.

Inclusion criteria

- Availability of technically adequate staging imaging: 1.5 or 3.0 T MRI and ^{18}FDG-PET-CT
- Histologically confirmed primary adenocarcinoma, squamous cell carcinoma or adeno-squamous carcinoma of the uterine cervix;
- Women with histologically confirmed FIGO stage IB (IB3 excluded) and IIA1 disease
- Women undergoing either a Type B or C radical hysterectomy according to Querleu Morrow classification
- ECOG Performance Status of 0, 1 or 2
- Patient must be suitable candidates for surgery.
- Patients who have signed an approved Informed Consent
- Age> 18 years

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Exclusion criteria

- Absence or technical inadequacy of staging imaging (1.5 or 3 T MRI and ^{18}FDG-PET-CT)
- Any histology other than adenocarcinoma, squamous cell carcinoma or adeno-squamous carcinoma of the uterine cervix
- Tumor size greater than 4 cm
- FIGO stage II-IV (except IIA1)
- Women with a history of pelvic or abdominal radiotherapy
- Women who are pregnant
- Women with contraindications to surgery
- Women with evidence of metastatic disease by conventional imaging studies, enlarged pelvic or aortic lymph nodes > 2cm; or histologically positive lymph nodes
- Serious concomitant systemic disorders incompatible with surgery or study (at the discretion of the investigator)
- Women unable to withstand prolonged lithotomy and steep Trendelenburg position
- Women with secondary invasive neoplasm in the last 5 years (except non-melanoma skin cancer, breast cancer T1 N0 M0 grade 1 or 2 without any signs of recurrence or activity)
- Women with iodine allergy cannot participate in the sentinel node part of the trial (not an exclusion criteria for the primary outcome)

3. Data exchange platform

Data collection and preprocessing strategies will be executed through the use of a program each institution will have to download from a central server. A graphical user interface (GUI) will allow the end-user to select specific directories to process. The aforementioned program will then subsequently anonymize any DICOM files it finds in those directories and processed files will then be uploaded to the central server for indexing and storage.
A web service will be set up in order to facilitate the storage and examination of all required files on the secure central server used by. In order to access all available services, the user is required to use a set of credentials unique to a specific institution. The aforementioned credentials will be provided on-demand by the system administrator, as no registration modules are provided for security and management reasons.
After successful validation of the login credentials, the user will be presented with the choice of either accessing a database specific to the user's institution (and subsequently modifying/deleting any files deemed necessary) or reviewing a summary of any information already available through the use of a dynamic dashboard.
Once deemed appropriate, a special account with administration rights will be able to download all uploaded files to an appropriate protected storage module and process them.
The radiomics analysis of the provided image sets will be performed using different image analysis platforms. The originating centers will be the sole responsible for the adherence to Patients' privacy preserving policies.

4. Radiomics analysis

The extraction of the radiomics features from the provided image sets will be performed using the MODDICOM platform (KBO labs, Rome, Italy), compliant with "The Image Biomarker Standardization
Initiative: Standardized Quantitative Radiomics for High-Throughput Image-based Phenotyping" principles. Both MR and ^{18}FDG-PET-CT images will be considered for the purposes of this study. More specifically the following MRI sequences will be used Ax T2, DWI. Both 1.5 and 3 T images will be allowed and possible local protocols will be evaluated on a case-by-case basis.

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PET-CT images will be evaluated using a dedicated fusion and display software (Syngovia by Siemens). Firstly, FDG-PET/CT interpretation will be based on visual assessment of FDG uptake. Subsequently, semi-quantitative parameters will be evaluated. According to literature, SUV is defined as standardized uptake value: SUVmax is the maximum SUV in each lesion, SUVmean is the mean SUV in each lesion. MTV is defined as the volume of the lesion with an higher SUVmax than established thresholds (e.g. higher than a background as mediastinal blood pool or liver right lobe; higher than 40%, 60% and 80% of SUVmax, respectively). TLG is estimated as the product of lesion SUVmean and MTV values. According to literature, total MTV and TLG (tMTV and tTLG) are calculated as the sum of MTV and TLG for all FDG-avid lesions, respectively.
The gross tumor volume will be contoured manually in all the image sets using a dedicated 3D segmentation software (i.e. 3D slicer), either by the originating center radiology/nuclear medicine team or by a team of expert users of the radiomics analysis center (Gemelli).
All features will be computed both in their 2D (averaging "by slice, without merging") and merged versions and different levels of discretization will be tested, on a case-by-case basis, for features performance optimization.
The following family of features will be extracted: Intensity-based statistical features; Morphological features; Texture features - Grey level co-occurrence based features; Texture features - Grey level run length based features; Texture features - Grey level size zone based features; Fractal dimension features.

4.1 Radiomics features selection and classifiers setup

For any univariate analysis, the features space dimensionality will be reduced with appropriate techniques and adequate any verification tests feature reproducibility analysis will be carried out in order to identify less reproducible features). Feature-outcome association will be then tested via Wilcoxon-Mann-Whitney tests for non-normally distributed features (e.g., normality hypothesis rejected with Shapiro test) or t-tests, where applicable.
The threshold for statistical significance will be considered as a p-value of 0.05. Multiple feature selection and model strategies will be exploited in order to set up radiomics based predictive models, e.g., applicable regression analyses (e.g., Logistic, Linear), radial kernel support vector machines and tree-based models with extensive grid search on the hyperparameter space analyses.

5. Ethical aspects

All the enrolled patients will be asked to fill-out and sign an informed consent form pertaining data collection, data custody and perspective handling for big data and machine learning analysis.
A dedicated web-service, GDPR compliant by design, will be set up in order to facilitate the storage and examination of all required pseudo anonymized files on the secure central server.
In order to access all available services, the user is required to use a set of credentials unique to a specific unit. The aforementioned credentials will be provided on-demand by the system administrator, as no registration modules are provided for security and management reasons.
The responsible investigators will ensure that the study will be conducted in agreement with the Declaration of Helsinki and following amendments, the laws and the specific regulations in force.
The competent ethics committee for each involved institution must validate informed consent documents before the single center can join the study.
The data originating centers will be the sole responsible for the adherence to Patients' privacy preserving policies and pseudo anonymization correct procedure.
The participation to this study is voluntary and patients are allowed to refuse further participation in any moment, with no prejudice for patient's care.
The benefits expected for the single patient are represented by the possibility to set up decisional support systems realized on images that have already been acquired for standard practice, thus optimizing resources and achieving an automatized quantitative analysis of the provided images.

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