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# Oncologic and reproductive outcome and Quality of Life after robot-assisted surgery for early stage cervical cancer

Evaluation of radical hysterectomy and radical trachelectomy

LINNEA EKDAHL

OBSTETRICS AND GYNECOLOGY | FACULTY OF MEDICINE | LUND UNIVERSITY



Radical hysterectomy and radical trachelectomy are complex surgical procedures. A woman with an early cervical cancer should be offered an individualized treatment that is oncologically safe. Offering information on different surgical approaches and their advantages and disadvantages and the possible impact on the womans future health and quality of life is important. The organization of care and surgical experience should be taken into account when choosing the surgical approach.

# Oncologic and reproductive outcome and Quality of Life after robot- assisted surgery for early stage cervical cancer.

Evaluation of radical hysterectomy and radical  
trachelectomy.

Linnea Ekdahl



**LUND**  
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<b>Oncologic and reproductive outcome and Quality of Life after robot-assisted surgery for early stage cervical cancer.</b> <b>Evaluation of radical hysterectomy and radical trachelectomy.</b>		
<p>The standard surgical treatment for early stage cervical cancer is a radical hysterectomy with pelvic lymphadenectomy. Radical trachelectomy (RRT) is an option in patients interested in future fertility and with tumors <math>\leq 2</math>cm. Robotic surgery for gynecological cancer was introduced in Lund, Sweden, in 2005 and since then the technique have emerged to also include identification of sentinel lymph nodes. Two international publications have raised concerns regarding the oncologic safety of robot assisted radical hysterectomy (RRH). The overall aim of this thesis is to evaluate the oncologic outcome after RRH and RRT in addition to reproductive outcome and quality of life after RRT.</p> <p><b>Study I:</b> A nationwide study to compare overall survival (OS) and disease-free survival (DFS) between 236 open and 628 robot-assisted radical hysterectomies. The 5-year OS was 92% and 94% and DFS was 84% and 88% for the open and robot-assisted cohorts, respectively. Propensity score analysis, matched for seven parameters, found no significant differences in survival rates between the groups.</p> <p><b>Study II:</b> A nationwide study to evaluate the impact of institutional surgical experience on recurrence rate following RRH for early stage cervical cancer. Among the 489 women who did not receive adjuvant radio chemotherapy (RC-T), the rate of recurrence was 3.6% in the experienced cohort (&gt;50 procedures) compared to 9.3% in the introductory cohort (<math>p &lt; 0.05</math>). This was also seen in tumors <math>&lt; 2</math> cm regardless of RC-T (<math>p &lt; 0.05</math>). The rate of postoperative complications decreased with increased institutional surgical experience.</p> <p><b>Study III:</b> A multicenter international study to evaluate long term oncologic and reproductive outcome following fertility sparing RRT. The oncologic outcome of the 166 women included, with 4.8% node positivity, was a recurrence rate of 7.2%. Pregnancy rate was 80%. There were 81 pregnancies beyond first trimester and 76 live babies of which 54 (70 %) were delivered at term and 65 (86%) delivered gestational week (GW) <math>\geq 32+0</math>. The recurrence rate is comparable to the IRTA study and larger individual studies of vaginal radical trachelectomy.</p> <p><b>Study IV:</b> A multicenter international evaluation of factors potentially associated with reproductive outcome following RRT. Of women prescribed an oral metronidazole regime from GW 15+0 to 21+6 2/22 (9%) pregnancies beyond the first trimester were prematurely delivered compared with 13/31 (42%) pregnancies resulting in a second trimester miscarriage or a premature delivery when the regime was not applied. With a regime of oral metronidazole/no sexual intercourse in pregnancies after RRT a four-fold reduction in second trimester miscarriage and premature Cesareans was observed.</p> <p><b>Study V:</b> A Single institution evaluation of long term clinical outcome and quality of life following RRT. None of the 42 women with a completed RRT recurred. The median GHS score was 75. 48% of patients reported worry of dyspareunia. Lymphoedema was reported in 45%. Pregnancy rate was 79%. This single institution evaluation present excellent oncologic and fertility outcome. The women's quality of life was affected postoperatively, particularly with regards to their sexual well-being and lymphatic side-effects.</p>		
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Evaluation of radical hysterectomy and radical  
trachelectomy

Linnea Ekdahl



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**MADE IN SWEDEN** 

*To Ida, Felix, Jesper and Martin*



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## Thesis at a glance

Study I	Aim	Results	Conclusion
<p>Study I: No survival difference between robotic and open radical hysterectomy for women with early-stage cervical cancer: results from a nationwide population-based cohort study.</p> <p>Study II: Increased Institutional Surgical Experience in Robot-Assisted Radical Hysterectomy for Early Stage Cervical Cancer Reduces Recurrence Rate: Results from a Nationwide Study</p> <p>Study III: Long term oncologic and reproductive outcomes after robot-assisted radical trachelectomy for early-stage cervical cancer. An international multicenter study.</p>	<p>To compare overall survival (OS) and disease-free survival (DFS) after open (ORH) and robotic radical hysterectomy (RRH) for early-stage cervical cancer.</p> <p>To evaluate the impact of institutional surgical experience on recurrence following robotic radical hysterectomy (RRH) for early stage cervical cancer.</p> <p>Long term oncologic and reproductive outcome following fertility sparing robot-assisted radical trachelectomy (RRT).</p> <p>Evaluation of factors potentially associated with reproductive outcome following fertility sparing robotic radical trachelectomy (RRT) in cervical cancer.</p>	<p>In 864 women (236 open and 628 robotic) the 5-year OS was 92% and 94% and DFS was 84% and 88% for the open and robotic cohorts, respectively. Using propensity score analysis, matched for relevant parameters, no significant differences in survival rates between the groups was seen.</p> <p>Among the 489 women who did not receive adjuvant radio chemotherapy (RC-T), the rate of recurrence was 3.6% in the experienced cohort (&gt;50 procedures) compared with 9.3% in the introductory cohort (<math>p &lt; 0.05</math>). This was also seen in tumors &lt; 2 cm regardless of RC-T (<math>p &lt; 0.05</math>).</p> <p>166 women were included with 4.8% node positivity. At a median follow up of 58 months, 12 women (7.2 %) had recurred. Pregnancy rate was 80%. There were 81 pregnancies beyond the first trimester and 76 live babies of which 54 (70 %) were delivered at term and 65 (86%) delivered at gestational week (GW) <math>\geq 32+0</math>.</p> <p>In pregnancies where a regime of oral metronidazole from GW 15+0 -21+6 and sexual abstinence from GW 15+0 was prescribed 2/22 (9%) had a premature delivery compared with 13/31 (42%) when the regime was not applied (<math>p=0.009</math>). A short postoperative non pregnant cervical length was associated with a lower conception rate (<math>p =0.04</math>).</p>	<p>In a complete nationwide population-based cohort, where RRH for early-stage cervical cancer is highly centralised, neither long-term survival nor pattern of recurrence differed significantly between open and robotic surgery.</p> <p>The rate of recurrence following RRT for early stage cervical cancer decreased with increased institutional surgical experience, in tumors &lt; 2 cm and in women who did not receive adjuvant RC-T.</p> <p>The recurrence rate in this study is comparable to the recurrence rate after minimally invasive trachelectomy stated in the IRTA study and in larger individual studies of vaginal radical trachelectomy. The high pregnancy rate and low rate of premature delivery before GW 32+0 underlines the feasibility of the robot-assisted approach.</p>
<p>Study IV: A combination of second trimester oral metronidazole and no sexual intercourse during second and third trimester may reduce late miscarriage and premature delivery after fertility sparing radical trachelectomy.</p> <p>Study V: Quality of Life and long-term clinical outcome following robot-assisted radical trachelectomy.</p>	<p>Evaluation of factors potentially associated with reproductive outcome following fertility sparing robotic radical trachelectomy (RRT) in cervical cancer.</p> <p>Evaluation of long term clinical outcome following robotic radical trachelectomy (RRT) including Quality of Life, sexual function and lymphedema.</p>	<p>A four-fold reduction in second trimester miscarriages and premature Cesareans in pregnancies after RRT was observed, after oral metronidazole/no sexual intercourse regime. A short postoperative non pregnant cervical length was associated with impaired fertility.</p> <p>None of the 42 women with a completed RRT recurred. The median GHS score was 75. 48% of patients reported worry of dyspareunia. Lymphoedema was reported in 45%. Pregnancy rate was 79%. A metronidazole/no sexual intercourse regime was applied in 26 of 28 pregnancies, resulting in a 92% term (<math>\geq</math>GW 36+0) delivery rate.</p>	<p>A four-fold reduction in second trimester miscarriages and premature Cesareans in pregnancies after RRT was observed, after oral metronidazole/no sexual intercourse regime. A short postoperative non pregnant cervical length was associated with impaired fertility.</p> <p>RRT in this single institution study was associated with excellent oncologic and obstetric outcomes. Women's quality of life was affected postoperatively, particularly with regards to their sexual well-being and lymphatic side-effects.</p>

# Original papers

This thesis is based on the following original papers, which will be referred to in the text by their Roman numerals. The papers are appendixd at the end of the thesis.

I. Alfonzo E, Wallin E, **Ekdahl L**, Staf C, Rådestad AF, Reynisson P, Stålberg K, Falconer H, Persson J, Dahm-Kähler P. No survival difference between robotic and open radical hysterectomy for women with early-stage cervical cancer: results from a nationwide population-based cohort study. *European Journal of Cancer*. 2019; 116:169-177.

II. **Ekdahl L**, Wallin E, Alfonzo E, Reynisson P, Lönnerfors C, Dahm-Kähler P, Falconer H, Persson J. Increased Institutional Surgical Experience in Robot-Assisted Radical Hysterectomy for Early Stage Cervical Cancer Reduces Recurrence Rate: Results from a Nationwide Study. *Journal of Clinical Medicine*. 2020; 9(11):3715.

III. **Ekdahl L**, Paraghamian S, Eoh K J, Thumuluru KM, Butler-Manuel S, Kim Y T, Boggess J F, Persson J, Falconer H. Long term oncologic and reproductive outcomes after robot-assisted radical trachelectomy for early-stage cervical cancer. An international multicenter study. Manuscript unpublished.

IV. **Ekdahl L**, Eoh K J, Thumuluru KM, Butler-Manuel S, Kim Y T, Falconer H, Persson J. A combination of second trimester oral metronidazole and no sexual intercourse during second and third trimester may reduce late miscarriage and premature delivery after fertility sparing radical trachelectomy. *European Journal of Obstetrics and Gynecology and Reproductive Biology*. 2021; 265:90-95.

V. **Ekdahl L**, Crusensvärd M, Reynisson P, Lönnerfors C, Persson J. Quality of Life and clinical outcome following robotic radical trachelectomy. Submitted after review to *European Journal of Obstetrics and Gynecology and Reproductive Biology*.

# Populärvetenskaplig sammanfattning

Globalt är livmoderhalscancer (cervixcancer) den fjärde vanligaste cancerformen hos kvinnor och den vanligaste gynekologiska cancerformen med höga incidenssiffror i synnerhet i utvecklingsländer. I Sverige är sjukdomen relativt sett ovanligare men drabbar fortfarande cirka 550 kvinnor årligen varav två tredjedelar i så tidigt stadium att man kan behandla kirurgiskt medan strålbehandling rekommenderas i mer avancerade stadier.

Kirurgisk behandling innebär i normalfallet att hela livmodern opereras bort med marginaler mot frisk vävnad (radikal hysterektomi) samtidigt med en utrymning av lymfkörtlar i bäckenet. Sedan 2006 har flertalet radikala hysterektomier i Lund utförts med operationsrobot, en typ av mer exakt titthålskirurgi, vilket anses ha fördelar med kortare vårdtider och färre komplikationer jämfört med öppen radikal hysterektomi (ORH) och kortare operationstider än traditionell titthålskirurgi som ofta anses för komplicerad.

Om det finns ett önskemål om bevarad fertilitet och om tumören är liten och belägen i den yttre delen av livmoderhalsen kan fertiliteten bevaras via ett speciellt ingrepp, radikal trakelektomi, vilket innebär att större delen av livmoderhalsen tas bort och att vagina sys tillbaka till resterande livmoder. För att minska risken för förtidsbörd görs en förstärkning av livmoderhalsen med en permanent sutur (inre cerclage) varefter förlossning måste ske med kejsarsnitt. Även vid detta ingrepp genomförs lymfkörtelutrymning i bäckenet. Risken för återfall och påverkan på fertilitet på lång sikt samt risken för förtidsbörd och påverkan på livskvalitet, sexuell funktion och lymfödem är otillräckligt studerat efter trakelektomi.

Risken för återfall vid livmoderhalscancer beror huvudsakligen på om tumören spritt sig till lymfkörtlarna liksom på tumörens storlek. Vid spridning till lymfkörtlarna, vid otillräckliga marginaler till frisk vävnad efter kirurgi eller vid oväntat stora tumörer ges onkologisk efterbehandling i form av strålning med tillägg av cellgift. Efter lymfkörtelutrymning finns en risk att utveckla lymfsvullnad i benen vilket orsakar ett livslångt lidande och lymfterapeutiska åtgärder.

Avhandlingens målsättning är att utvärdera onkologiskt och reproduktivt utfall samt livskvalité och kroppsfunction efter robot assisterad kirurgisk behandling vid tidig livmoderhalscancer.

**Studie I** jämför återfallsfrekvens och överlevnad efter radikal hysterektomi med lymfkörtelutrymning utförd som öppen (ORH) eller robotassisterad (RRH) kirurgi. Studien inkluderade 864 kvinnor opererade för tidig livmoderhalscancer mellan 2011 och 2017 i Sverige. Studien, som baseras på det svenska kvalitetsregistret för gynekologisk cancerkirurgi som startades 2008 och inkluderar cervixcancer sedan 2011, motiverades av att en lägre återfallsrisk efter öppen kirurgi hade beskrivits i två internationella studier, en amerikansk registerstudie och en internationell studie där man lottat patienter till öppen eller minimalinvasiv kirurgi. Resultaten gjorde att många länder, inklusive Sverige därefter rekommenderar öppen kirurgi som förstahandsval. Våra resultat från studie I visar att robotassisterad radikal hysterektomi är onkologiskt lika säker som öppen teknik i svenska förhållanden med delvis centralisering.

I **studie II** undersökte vi om kirurgisk erfarenhet påverkar risken för återfall efter RRH vid tidig livmoderhalscancer. Studien inkluderade alla 635 kvinnor som genomgått RRH i Sverige från 2005 till juni 2017, och inkluderade därför tidiga resultat från de kliniker som startat robotkirurgi innan 2011. Vi studerade en brytpunkt på 50 RRH per institution efter vilken risken för återfall och även allvarliga postoperativa komplikationer minskade. Resultaten kan eventuellt förklara den sämre överlevnad som setts efter RRH i internationella studier som ofta genomförts när RRH var under en introduktionsperiod och/eller på centra med ett litet årligt antal av RRH. Resultaten pekar på vikten av strukturerad implementering av en ny operationsteknik samt betydelsen av eventuell ytterligare centralisering.

**Studie III-IV** utvärderar långtids fertilitet och onkologiskt utfall efter robotassisterad radikal trakelektomi (RRT) utförda med liknande operationsteknik mellan 2007 och 2019 vid centra i Europa, Asien och Nordamerika mellan 2007 och 2019. I **studie III** fann vi att 9 av 149 (6%) kvinnor med en fullständig RRT fick återfall i sin tumörsjukdom vilket överensstämmer med resultat från trakelektomi med andra kirurgiska tekniker och liknande uppföljningstid och riskprofil. Fertilitetsresultaten var högre (80%) än rapporterat i större samlingsmaterial och andelen födda efter graviditetsvecka 32 var 86% vilket också är en internationellt hög siffra. I **studie IV** såg vi att en kort kvarvarande livmoderhals efter RRT ökar risken att inte lyckas bli gravid efter trakelektomi. Ett mycket viktigt fynd var att en fyrfaldig minskning av risken för förtidsbörd noterades för kvinnor opererade vid kvinnokliniken i Lund som tillämpat en förebyggande antibiotika-behandling mot en avvikande bakterieflora i slidan liksom samlagsförbud under den senare delen av graviditeten. Även om resultaten baseras på ett retrospektivt material är skillnaden så stor att vi anser att denna behandling, som är ofarlig för fostret, skall införas som rutin framgent även på andra kliniker och bekräftas med prospektiva undersökningar.

**Studie V** utvärderar onkologiska och reproduktiva resultat för de 49 kvinnor som genomgått RRT i Lund mellan åren 2007 och 2020, med ytterligare fokus på livskvalitetsmätt utvärderade genom validerade frågeformulär. Studien visar på en

låg återfallsrisk och ger ytterligare data som stödjer den mycket låga prematuritetsfrekvens vi sett med den förebyggande behandlingen i studie IV. Vi fann att livskvalité och sexuell funktion kan påverkas negativt efter trakelektomi samt att 45% upplevde lymfödem efter RRT. Studien bidrar med den bredare bild av effekterna av en RRT vilket är viktigt för att kunna ge kvinnor rätt förväntningar inför ett fertilitetsbevarande ingrepp. RRT.



# Abstract

## *Background:*

More than 500 women are diagnosed with cervical cancer in Sweden each year and approximately 65% are candidates for primary surgery. The recommended surgical treatment for early stage cervical cancer is a radical hysterectomy (RH) and pelvic lymphadenectomy. In selected women with a wish for preserved fertility and tumors  $\leq 2$ cm radical trachelectomy (RT) is an optional surgical approach.

Robotic surgery for gynecological cancer was introduced in Sweden in 2005 offering minimal invasive surgery and its associated advantages to women previously operated by open surgery. In 2018 two international publications raised concerns regarding the oncologic safety of laparoscopy and robot assisted radical hysterectomy (RRH) for early stage cervical cancer.

The overall aim of this thesis was to evaluate the oncologic outcome after RRH and robotic radical trachelectomy (RRT) and the reproductive outcome and quality of life after RRT.

## *Aims of the studies:*

*Study I:* To compare disease free survival (DFS) and overall survival (OS) after open radical hysterectomy (ORH) and RRH for early stage cervical cancer in Sweden.

*Study II:* To investigate the effect of increased surgical experience, per institution, on recurrence rate and surgical complications after RRH.

*Study III:* To evaluate long-term oncologic outcome, reproductive outcome and postoperative complications following fertility sparing RRT.

*Study IV:* To investigate factors and regimes possibly associated with second trimester miscarriage and premature delivery following fertility sparing RRT.

*Study V:* To evaluate quality of life, sexual function and lymphedema as well as other long-term clinical outcomes following RRT.

## *Material and methods*

*Study I:* A nationwide cohort study including all women  $\geq 18$  years with FIGO stage IA1-IB1 cervical cancer having a primary RH performed in Sweden between January 2011 and December 2017. Survival rates were compared between open and robotic approach.

*Study II:* A study including all women who underwent a RRH for stage IA2-IB1 cervical cancer at tertiary referral centers in Sweden from its implementation in December 2005 until June 2017. The material was divided into early and late cohorts per institution and rate of recurrences and surgical complications were compared between groups.

*Study III:* Consecutive women planned for RRT according to guidelines at five international referral centres between 2007 and 2019 were included. The RRTs were similarly performed sparing the uterine arteries and with the use of an internal cervical cerclage. Perioperative and follow up data were retrieved. Long term oncologic, reproductive and surgical outcome was assessed.

*Study IV:* Consecutive women with a completed RRT at four international referral centres between 2007 and 2019 were included. An internal cervical cerclage was placed. Factors possibly related to fertility and premature delivery were assessed.

*Study V:* Consecutive women with a planned RRT at Skåne University Hospital, Lund, between 2007 and 2020 were included. The answers to validated questionnaires (QLQ-C30, QLQ-CX24 and LYMQOL) regarding quality of life, sexual function and lymphoedema were analysed. Oncologic and reproductive outcome as well as postoperative complications were assessed.

## *Results and conclusions*

*Study I:* Of 864 included women, 628 (73%) underwent RRH and 236 (27%) ORH. The majority (814/864) of the surgeries were performed at a tertiary center. There was no difference in the 5-year OS with 92% in the open group and 94% in the robotic group. Similarly, there was no difference in the 5-year DFS with 84% in the open group and 88% in the robotic group. In the propensity score analysis, the 232 matched women showed no survival differences between the surgical approaches (85% vs 84%).

- In settings where radical hysterectomy for early-stage cervical cancer is highly centralized, robotic radical hysterectomy appears oncologically safe.

*Study II:* A statistical model indicated a decreased probability of recurrence with increased experience with a cut-off at approximately 50 procedures. The first 50 RRHs (introductory cohort) from each of the six hospitals were compared with the remaining  $>50$  RRHs (experienced cohort) from the most experienced hospitals. Among the 489 women who did not receive adjuvant radio chemotherapy (RC-T),

the rate of recurrence was 3.6% in the experienced cohort (>50 procedures) compared to 9.3% in the introductory cohort ( $p < 0.05$ ).

- The rate of recurrence following RRH for early stage cervical cancer decreased significantly with increased institutional surgical experience in women who did not receive adjuvant RC-T. Studies on RRH and organization of care should consider the negative impact of low volume surgeons and early adopters on the rate of recurrence.

*Study III:* 166 women were included (4.8% node positivity) and at a median follow up of 58 months, 12 of all women (7.2 %) and 9 (6.0%) of women with a completed RRT had recurred. The pregnancy rate was 80% and of the 76 live births, 54 (70 %) were delivered at term and 65 (86%) were delivered at gestational week (GW)  $\geq 32+0$ .

- In this long-term follow-up of RRT the recurrence rate is comparable to studies with similar tumor risk profile and follow-up time. The high pregnancy rate and low rate of premature delivery before GW 32+0 underlines the feasibility of the robot-assisted approach.

*Study IV:*

In pregnancies where a regime of oral metronidazole from GW 15+0 -21+6 and sexual abstinence from GW 15+0 was prescribed 2/22 (9%) had a premature delivery compared with 13/31 (42%) when the regime was not applied ( $p=0.009$ ). A short postoperative non pregnant cervical length was associated with a lower conception rate ( $p =0.04$ ).

- An second trimester oral metronidazole regime combined with no sexual intercourse during pregnancy may reduce second trimester miscarriage and premature deliveries in pregnancies after RRT. A short postoperative non pregnant cervical length was associated with impaired fertility.

*Study V:* None of the 42/49 women with a completed RRT recurred. Sexual/vaginal functioning in the symptom scale had a median score of 25 of 100 in the questionnaire and 48% of patients reported worry of dyspareunia. Lymphoedema was reported in 45%, where 9% reported severe symptom. There were no intraoperative or postoperative complications CD  $\geq$  grade III. Of women who attempted to conceive 79% were successful. An oral metronidazole/no sexual intercourse regime (described in study IV) was applied in 26/28 pregnancies resulting in a 92% term ( $\geq$ GW 36+0) delivery rate.

- This single institution RRT was associated with a low recurrence rate, a high fertility rate and an exceptionally high term delivery rate. The women's quality of life was affected postoperatively, particularly with regards to their sexual well-being and lymphatic side-effects.

# List of abbreviations

<b>ART</b>	Abdominal radical trachelectomy
<b>CD</b>	Clavien Dindo classification
<b>DFS</b>	Disease free survival
<b>GW</b>	Gestational week
<b>KUH</b>	Karolinska University Hospital
<b>LRT</b>	Laparoscopic radical trachelectomy
<b>LVSI</b>	Lymph vascular space invasion
<b>MI-RT</b>	Minimally invasive radical trachelectomy
<b>MIS</b>	Minimally invasive surgery
<b>ORH</b>	Open radical hysterectomy
<b>OS</b>	Overall survival
<b>QOL</b>	Quality of life
<b>RC-T</b>	Radio chemotherapy
<b>RRH</b>	Robot-assisted radical hysterectomy
<b>RRT</b>	Robot-assisted radical trachelectomy
<b>RSCH</b>	Royal Surrey County Hospital
<b>RH</b>	Radical hysterectomy
<b>RT</b>	Radical trachelectomy
<b>SLN</b>	Sentinel lymph node
<b>SUH</b>	Skåne University Hospital, Lund
<b>UNC</b>	University of North Carolina Chapel Hill
<b>VRT</b>	Vaginal radical trachelectomy
<b>YUHS</b>	Yonsei University College of Medicine

# Introduction

A majority of women diagnosed with cervical cancer are of childbearing age. Several factors influence cancer prognosis including grade, stage and responsiveness to treatment. In Sweden, surgery is the primary treatment in approximately 65% of women diagnosed with cervical cancer (RCC 2019) and the recommended procedure is a radical hysterectomy (RH) including a pelvic lymphadenectomy. A RH alleviates the possibility of future pregnancy and in addition carries a risk of both short and long time side effects. Consequently, being diagnosed with cervical cancer has a major impact on the womans present and future life. In women with early stage cervical cancer who wish to preserve fertility a radical trachelectomy (RT) is an optional surgical approach. RT involves removal of the cervix, parametrium and vaginal cuff, while retaining the uterine arteries, uterine fundus, isthmus/upper cervix and adnexa.

In Sweden, robot-assisted surgery for cervical cancer was introduced in 2005 and gradually became the preferred surgical approach. In 2018, two international studies demonstrated inferior survival rate after minimally invasive RH, including robot-assisted technique, compared to open radical hysterectomy (ORH). This led to changes in the National Comprehensive Cancer Network (NCCN 2019) and the European Society of Gynecological Oncology (ESGO 2019) treatment guidelines where ORH is recommended as the preferred surgical approach. For RT, the International Radical Trachelectomy Assessment (IRTA) study published in 2021 found no difference in recurrence rate between abdominal RT and minimal invasive RT (Salvo et al. 2021).

This thesis sought to evaluate the oncologic outcome after robot-assisted radical hysterectomy (RRH) from a national Swedish perspective. In addition, the long term oncologic and reproductive outcome as well as postoperative complications and quality of life after robot-assisted radical trachelectomy (RRT) was investigated.



# Background

## Cervical cancer

### Epidemiology and etiology

Globally, cervical cancer is the fourth most common cancer among women, with an estimated 604,000 new cases diagnosed in 2020 (Sung H et al. 2021). In 2018, nearly 90% of the 311,000 deaths due to cervical cancer occurred in low-to-middle-income countries, where the highest regional incidence and mortality was seen in sub Saharan Africa. (Ferlay et al. 2019) (Figure 1). Every year more than 500 women are diagnosed with cervical cancer in Sweden (RCC, 2020).

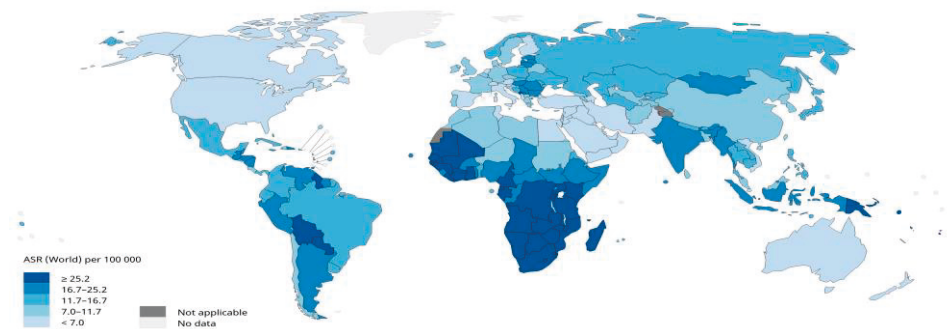


Figure 1. Estimated age-standardized incidence rates (World) in 2020, cervix uteri, females, all ages. Data source GLOBOCAN 2020. Graph production: IARC (<http://qco.iarc.fr/today>) World Health Organization.

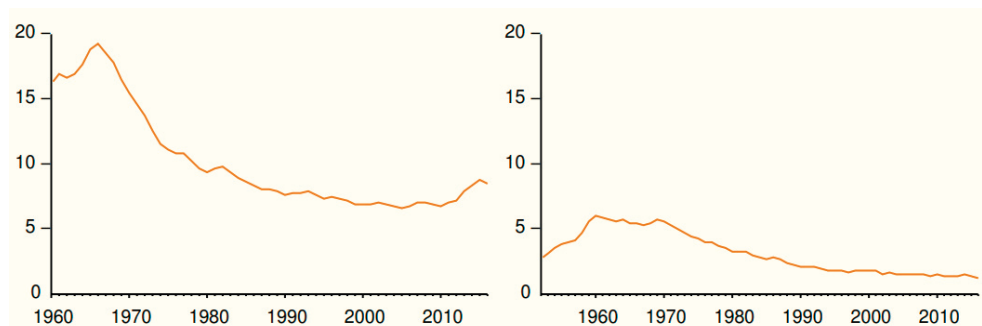
A majority of cervical cancers is caused by persistent Human Papilloma virus (HPV) infection (Walboomers et al. 1999, Lagheden et al. 2018, Arroyo et al. 2020). Oncoproteins E6 and E7 in high-risk HPV will promote cell proliferation and inactivate tumour suppression pathways causing uncontrolled growth in basal epithelial cells of the cervix (McBride 2017). HPV type 16 and 18 can be found in 71 % of all cervical cancer and HPV 16, 18 and 45 can be found in 94% of all adenocarcinomas (de Sanjose et al. 2010). HPV is mainly transmitted through sexual contact and most prevalent among women in their twenties (Schiffman et al. 2013). The majority of sexually active women will be infected at least once and approximately 90% of HPV infections usually clear up within 1-2 years after



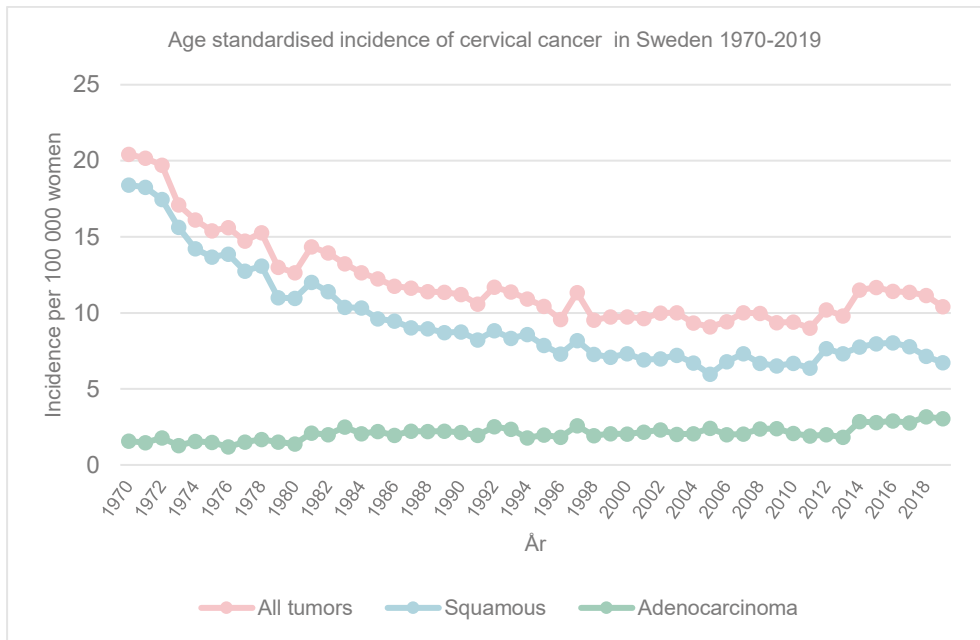
acquisition (RCC 2021). Immunodeficiency due to medication or for example HIV infection increases the risk of a persistent infection (Palefsky 2009). A persistent infection in combination with associated risk factors such as smoking, oral contraceptives and other sexually transmitted diseases predisposes for the development of precancerous lesions (Castellsagué et al. 2002, Silins et al. 2005). The progression rate of untreated high-grade intraepithelial neoplasia (HSIL) to cervical cancer is 12-31% (Mc Credie et al. 2008) whereas the regression rate of low-grade intraepithelial neoplasia (LSIL) is 60% (Oster 1993). Sexual debut at a young age and multiple sexual partners increase the risk of cervical cancer (La Vecchia et al. 1986). HPV vaccination was included in the Swedish vaccination programme for girls age 10-12 years in 2010, and for boys since 2020. It is efficacious in the prevention of infection and decreases the risk of precancerous lesions and cervical cancer (Lei 2020, Castellsagué et al. 2011, Jiayao et al. 2020). If vaccination and screening programmes are not implemented in low-income countries, over 44 million women will be affected by cervical cancer in the next 50 years (Simms et al. 2019).

## Prevention

Cytology-based cervical cancer screening was implemented in Sweden in 1965 and has led to a reduction in the incidence of cervical cancer from 25 cases/100 000 in 1965 to 8,4/100 000 in 2012 (NKCx 2017) (Figure 2). Despite a well implemented screening program, an increase in the incidence of adenocarcinoma was noted in Sweden in 2014-2018 (Dillner et al. 2018, Wang et al. 2020) (Figure 3). However, new strategies in the cytology laboratories were implemented and a report in the Swedish Läkartidningen in September 2020 states that the trend of increase might be broken. The Swedish guidelines for cervical cancer prevention from 2021 recommend primary screening every third year with cytology for women age 23-29 and HPV analysis followed by cytology in case of HPV positivity every third year in women between 30–49 years and every seventh year in women between the age 50-64 (RCC 2021).



**Figure 2.** Incidence of cervical cancer /100 000 women (left) and mortality /100 000 women (right) in Sweden 1960-2020. Data source: NORDCAN <https://www-dep.iarc.fr/nordcan/dk/frame.asp>



**Figure 3.** Age standardised incidence of cervical cancer in Sweden per 100 000 women 1970-2019. With kind permission Professor Sparén.

## Symptoms and diagnosis

Primary symptoms in cervical cancer are irregular vaginal bleeding, often postcoital, or watery foul-smelling discharge from tumour necrosis. Locally advanced cancer can cause pelvic or abdominal pain and leg oedema due to compression of nerves and veins. Hydronephrosis due to tumour compression of the ureter can cause back pain. If a cervical cancer is suspected, either clinically or through cytology, histologic confirmation is necessary. According to national guidelines a preoperative pelvic MRI and a CT scan of the thorax and abdomen as well as an examination under general anaesthesia including a cystoscopy is needed. If fertility sparing surgery is a suitable option a vaginal ultrasonography is performed to measure the cervical length. A PET-scan is performed in more advanced stages when primary radio chemotherapy is the treatment of choice (RCC 2020).

## **Histopathology and Staging**

Squamous cell carcinoma account for 75 % of all cervical cancers whereas 25% are adenocarcinoma or adenosquamous. Clear cell, mucinous and neuroendocrine tumours are rare and are associated with a poorer prognosis (Tempfer et al. 2018).

The staging of cervical cancer is done according to the International Federation of Gynecology and Oncology (FIGO) classification. The FIGO staging from 2009 was based on clinical examination combined with cystoscopy, urography, rectoscopy and chest X-ray, all basic examinations that are more readily accessible in low resource settings. In 2018 a revised version was presented incorporating both lymph node status from imaging and histopathological results. This updated staging subdivides stage IB tumors into three groups depending on tumor size; all with stroma invasion  $\geq 5$ mm. It was implemented in Sweden in January 2020. The Classifications of Malignant Tumors (TNM), describes the size of the primary tumor (T), lymph nodes status (N) and distant metastases (M) and can be combined with the FIGO staging system (Amin MB et al. 2017) see Table 1.

**Table 1.** Comparison of TNM classification and FIGO staging 2009 and 2018 of cervical cancer. Adapted from Bhatla et al. 2018 and Wallin 2020. Changes are marked in red.

TNM	2018	2009	
T1	I	I	Carcinoma is strictly confined to the cervix (extension to the uterine corpus should be disregarded)
T1a		IA	Invasive cancer identified only microscopically (All gross lesions even with superficial invasion are Stage IB cancers). Stromal invasion is limited to maximal depth of 5 mm and width of 7 mm.
T1a1		IA1	Stromal invasion $\leq$ 3 mm in depth and $\leq$ 7mm in width
T1a1	IA1		Stromal invasion < 3 mm in depth
T1a2		IA2	Stromal invasion > 3 mm and $\leq$ 5 mm in depth and $\leq$ 7 mm in width
T1a2	IA2		Stromal invasion $\geq$ 3 mm and < 5 mm in depth
T1b		IB	Microscopic lesions > IA or macroscopic lesions limited to the cervix.
T1b	IB		Invasive carcinoma confined to the uterine cervix, with measured deepest invasion $\geq$ 5 mm. (> IA)
T1b1		IB1	Clinical lesions no greater than 4 cm in size
T1b1	IB1		Invasive carcinoma with $\geq$ 5mm stroma invasion and tumor dimensions measures <2 cm in greatest dimension
T1b2		IB2	Clinical lesions > 4cm in size
T1b2	IB2		Invasive carcinoma measures $\geq$ 2 cm and <4 cm in greatest dimension
T1b3	IB3		Invasive carcinoma measures $\geq$ 4 cm in greatest dimension
T2	II	II	Carcinoma invades beyond the uterus, but has not extended onto the lower third of the vagina or to the pelvic wall
T2a	IIA	IIA	Limited to the upper two-thirds of the vagina without parametrial involvement
T2a1	IIA1	IIA1	Tumor measures < 4 cm in greatest dimension
T2a2	IIA2	IIA2	Tumor measures $\geq$ 4 cm in greatest dimension
T2b	IIB	IIB	With parametrial involvement but not up to the pelvic wall
T3	III	III	Carcinoma involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or nonfunctioning kidney and/or involves pelvic and/or para-aortic lymph nodes
T3a	IIIA	IIIA	Involves the lower third of the vagina, with no extension to the pelvic wall
T3b	IIIB	IIIB	Extension to the pelvic wall and/or hydronephrosis or nonfunctioning kidney from tumor
TXN1	IIIC		Involvement of pelvic and/or para-aortic lymph nodes, irrespective of tumor size and extent
	IIIC1		Pelvic lymph node metastasis only
	IIIC2		Para-aortic lymph node metastasis
T4	IV	IV	Carcinoma has extended beyond the true pelvis or has involved (biopsy-proven) the mucosa of the bladder or rectum
T4a	IVA	IVA	Spread to adjacent pelvic organs
T4b	IVB	IVB	Spread to distant organs

Adapted from Batla et al 2018.

## Treatment

### *Radical hysterectomy*

In early stage cervical cancer surgery is the treatment of choice whereas radiochemotherapy is the primary treatment option in stage IB3 and IIA2-IVB. In stage IA1-IA2 the recommended treatment is a conisation or simple hysterectomy and in stage IB1-IB2 and IIA1 a radical hysterectomy (RH) is performed (QM type A, Table 2). Ovarian metastases are rare, but removal of the ovaries is recommended in adenocarcinoma or high risk tumours (Shimada et al. 2006).

One of the first to perform a RH was Ernst Wertheim in the late 19<sup>th</sup> century. The procedure was refined to include a radical excision of the parametrial tissue and a wider resection of the vesicouterine ligament by Hidekazu Okabayashi in Japan in the 1920s (Verleye et al. 2009). Joe Meigs further developed the Wertheim operation in the 1950s to include a pelvic lymphadenectomy (Meigs 1951). This resulted in improved survival rates and a nerve sparing technique was further developed to minimise morbidity. Several classification systems for RH have been presented to systematise the procedure according to the extent of the dissection and tissue removal and to simplify the communication between surgeons. Piver-Ruthledge presented five types of extended hysterectomies in the 1970s (Piver et al. 1974) and Querleu and Morrow presented their four-scale classification of RH (A to D) in 2008 using distinct landmarks and allowing for a nerve-sparing technique (Querleu et al 2008, Querleu et al 2017) (Table 2). A non-randomised study published in 2009 showed a high survival rate after a total mesometrical resection, with removal of the embryologically defined uterovaginal compartment (Hoeckel et al. 2009). The Querleu and Morrow classification best represents the surgical method that is most commonly utilized.

**Table 2.** Classification of radical hysterectomy according to Querleu-Morrow (Querleu et al 2008, Querleu et al 2017).

Type	Resection	Mobilization of the ureter	Lateral dissection	Vaginal resection	Involvement of the sacrotuterine ligament	Involvement of the vesicouterine ligament
<b>A</b>	Extrafascial	None	Close to the cervix	Minimal resection	Dissection close to the cervix	Dissection close to the cervix.
<b>B</b>	Modified radical	Partial	Medial to the ureter	10mm	Partial resection	Partial resection
<b>C1</b>	Classic radical	Complete	Lateral to the ureter. At the iliac vessels caudal part preserved	15-20mm	Transection at the rectum. Nerve sparing	Transection at the bladder. Nerve sparing
<b>C2</b>	Classic radical	Complete	Lateral to the ureter. At the iliac vessels including caudal part	15-20mm	Transection at the rectum. Hypogastric nerve is sacrificed.	Transection at the bladder. Bladder nerves sacrificed.
<b>D</b>	Lateral extended	Complete	At the exit of the <i>a. iliac interna</i> , with exposure of the root to <i>n. ischiadicus</i>	15-20mm	Transection at the rectum	Transection at the bladder

### *Radical trachelectomy*

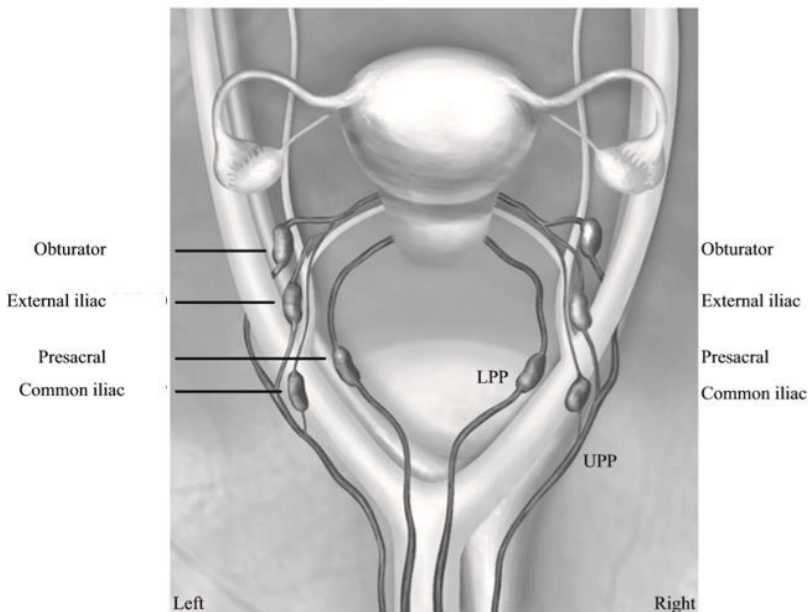
European Society of Gynaecological Oncology (ESGO) and National Comprehensive Cancer Network (NCCN) guidelines recommend fertility-sparing surgery involving conisation, simple or radical trachelectomy (RT) as an option in women with early stage cervical cancer (tumors  $\leq 2$ cm) and a wish for preserved fertility (Cibula et al. 2018, Koh et al. 2019). The trend of delayed childbearing has increased the demand for fertility-sparing treatment (Hamilton et al. 2015) and reports have shown an increased implementation of trachelectomy over the last few decades (Cui et al. 2018, Dostalek et al. 2018). RT was first described by Dargent in the early 1990s with a vaginal approach (VRT) combined with a laparoscopic pelvic lymphadenectomy (Dargent et al. 1995). Alternative approaches are abdominal RT via laparotomy (ART) and minimally invasive (MI-RT): laparoscopic (LRT) and robot assisted trachelectomy (RRT). The former has been preferred over a vaginal approach in larger tumors (Li et al. 2013). RRT was first described in a Swedish study in 2008 (Persson et al. 2008). The accuracy and reproducibility of the procedure have been studied and reports an equal level of cervical resection, but superior positioning of the cervical resection compared to vaginal trachelectomy (Persson et al. 2012).

A pelvic lymph node dissection preferably with a sentinel node (SLN) biopsy is performed to evaluate lymph node involvement. On frozen section all SLNs should be free of disease prior to proceeding further with the fertility sparing procedure. The paracolpium, lower parametria, and sacrouterine ligaments are dissected at adequate length. The descending branches of the uterine arteries are ligated but the main branches of the uterine arteries are spared. The cervix is transected and the vagina is divided securing a sufficient vaginal cuff. The removed cervical disc is sent to frozen section to ensure disease free surgical margins. The vagina is sutured to the remaining cervix and a permanent cerclage is placed.

A successful trachelectomy concept requires a preoperative cervical length allowing for resection of the tumour with sufficient margins, yet a remaining cervix of adequate length. The tumour needs to be situated at the distal part of the cervix and a preoperative estimation of the length of the cervix by ultrasonography or MRI in relation to tumour size and location is mandatory for selection of patients for RT. Although no absolute limit exists, the risk of premature labour is likely associated with the length of the remaining cervix where a post trachelectomy length of 10 mm or more is desired (Alvarez et al. 2018). An intraoperatively placed internal cervical cerclage may reduce the risk for premature birth but have the disadvantage of complicating management of second trimester miscarriage. Vaginal cerclages are rarely possible to place due to the lack of ectocervix after a trachelectomy. The association between development of a cervical stenosis and the use of an internal cerclage is unclear (Kim et al. 2014, Li et al. 2015).

### *Lymphatic anatomy and sentinel lymph node biopsy*

In the 19<sup>th</sup> century pelvic lymphatic anatomy was extensively studied in women who died of puerperal sepsis (Delamere 1904). Although pelvic lymphadenectomy has been a part of the staging procedure for gynecological cancers, more specific attention to the anatomy of the lymphatic drainage of the uterus came about when the sentinel node concept was introduced. Pelvic lymphatic anatomy was rediscovered and described in detail by Geppert et al. in 2017 who specified two separate lymphatic pathways; the upper paracervical pathway (UPP) and the lower paracervical pathway (LPP). The UPP follows the uterine artery to the medial external lymph nodes and/or obturator lymph nodes before crossing the external iliac artery and continuing lateral to the common iliac artery. The LPP runs along the sacrouterine ligament to the presacral area to presacral lymph nodes and thereafter medial to the common iliac artery. Both the UPP and LPP continues to the paraaortic and precaval area (Geppert B et al. 2017) (Figure 3).



**Figure 3.** Schematic overview of the pelvic uterine lymphatic pathways, UPP = upper paracervical pathway. LPP= lower paracervical pathway. With permission from Dr Geppert. (Geppert et al 2017).

A sentinel lymph node (SLN) biopsy followed by a full pelvic lymphadenectomy is suggested in stage 1A1 if lymph vascular space invasion (LVSI) is present and in all stage 1A2, 1B1-1B2 and 1A1 tumours.

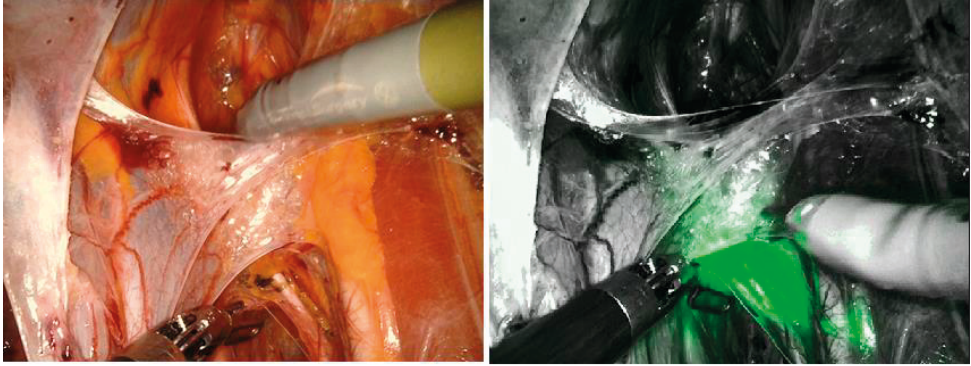
A full pelvic lymphadenectomy is associated with lymphatic complications; most commonly lymphedema. The wide range of incidence reported (3.7-47%) is partly



due to the absence of a standardized assessment tool and also influenced by the increase in cumulative incidence with time (Geppert et al. 2018, Hareyama et al. 2015). Lymphedema and associated symptoms have a negative impact on physical, functional and psychological well-being. The use of SLN biopsy can decrease the extent of the surgical procedure and associated adverse events while retaining information on lymph node involvement. Restricting the number of nodes allows for frozen section when applicable and possibility to perform ultra-sectioning and immunohistochemistry resulting in a more meticulous examination of the most important lymph nodes. An ideal SLN concept should be based on anatomy, have a high bilateral mapping rate and few false negative SLN (Persson et al. 2017). The upper paracervical lymphovascular tissue have been shown to contain metastases even in small tumors without other nodal involvement (Luhrs et al. 2021). It can be dissected without intraoperative morbidity and should be separately removed and included as SLN tissue. Technetium and patent blue dye has traditionally been used as tracer although Indocyanine Green (ICG) is the preferred tracer for SLN detection in endometrial and cervical cancer where a bilateral mapping rate of indocyanine green alone is shown to be 98.5% in experienced hands (Luhrs et al. 2020). In robot assisted surgery ICG may be used as a tracer in combination with the Fire-Fly® technology (Figure 5) (Geppert et al. 2017, Luhrs et al. 2020).

In cervical cancer the use of SLN biopsy and frozen section allows for the possibility to extend the procedure when applicable and abort the procedure in favour of radiochemotherapy in case of nodal metastases. The current guidelines recommend a full pelvic lymphadenectomy in > stage 1A1 cervical cancer.

Due to the relative rarity of the disease and the low risk of nodal disease in women with presumed early stage cervical cancer planned for surgery, adequately powered methodologically stringent prospective studies on sensitivity for an SLN-concept in cervical cancer have not yet been published. The Senticol II trial randomised women to either SLN and pelvic lymph node dissection (PLND) or SLN alone and found no difference in overall or disease free survival at a median follow-up of 51 months (Favre et al. 2021). A prospective study on the efficacy and sensitivity of an SLN-concept is currently ongoing at our institution [ NCT03680833] and results from the Senticol-III and Sentix trials are expected soon (Lecuru et al. 2019, Cibula et al. 2019). If future studies validate the oncological safety of an SLN-concept in cervical cancer, the positive impact on patient well-being cannot be underestimated.



**Figure 5.** Paravesical and pararectal spaces and upper parametrial tissue in a patient with endometrial cancer. On the right side using indocyanine green. With permission from Dr Geppert. (Geppert et al 2017).

### *Radio chemotherapy*

Radio chemotherapy (RC-T) is the primary treatment option in stage IB3 and IIA2-IVB. In Sweden, primary RC-T consists of external beam radiation (EBR) therapy of 45-56 Gray in combination with intracavitary radiotherapy (brachytherapy) and weekly Cisplatin (4-6x40mg/m<sup>2</sup>) (RCC 2020). In case of metastatic lymph nodes and/or insufficient margins perioperative or on final pathology adjuvant RC-T is administered with EBR and concomitant weekly Cisplatin. An recent trial found no difference in the risk of recurrence or death if completing the RH before RC-T or abandoning RH in favour of RC-T. The study recommends abandonment if positive lymph nodes are found perioperatively to reduce morbidity although whether this is valid for all tumor sizes remains unknown (Cibula et al. 2020). In radiation, intensity-modulated radiation therapy (IMRT) preferable with Volumetric Modulated Arc Therapy (VMAT) technology should be used to make the radiation more accurate, shorten treatment and reduce the overall dose of radiation (RCC 2020).

### **Outcome**

Radical hysterectomy was traditionally performed by abdominal or vaginal approach. The first laparoscopic radical hysterectomy (LRH) was performed in the early 1990s (Nezhat et al. 1992). Randomised controlled trials (RCTs) have shown similar survival rates but improved short term complications and length of stay after laparoscopic hysterectomy compared to laparotomy in endometrial cancer (Walker et al. 2009, Janda et al. 2017).

In 2005, the Food and Drug Administration (FDA) in the US, approved robot-assisted surgery for gynecologic diagnoses. That same year the first robot-assisted radical hysterectomy (RRH) was performed in Lund and one year later the first case report on RRH was published (Sert et al. 2006). Multiple publications have shown

a reduction in morbidity with decreased blood loss, fewer complications and shorter length of hospital stay compared to laparotomy (Boggess et al. 2008, Magrina et al. 2008, Maggioni et al. 2009). In comparison to traditional laparoscopy the robotic technique offers improved precision and ergonomics for the surgeon and a possibility to perform more complex procedures with a lower conversion rate (Nie et al. 2017, Lönnerfors et al. 2015, Landeen et al. 2011, Mäenpää et al. 2016, Jonsdottir et al. 2011, Gehrig et al. 2008). A Swedish study regarding health care costs found that after a substantial implementation period and a prerequisite of approximately 400 robot-assisted procedures annually RRH had an equal hospital cost to open radical hysterectomy (ORH) (Reynisson et al. 2013). The implementation of RRH in Sweden can be seen in Figure 4.

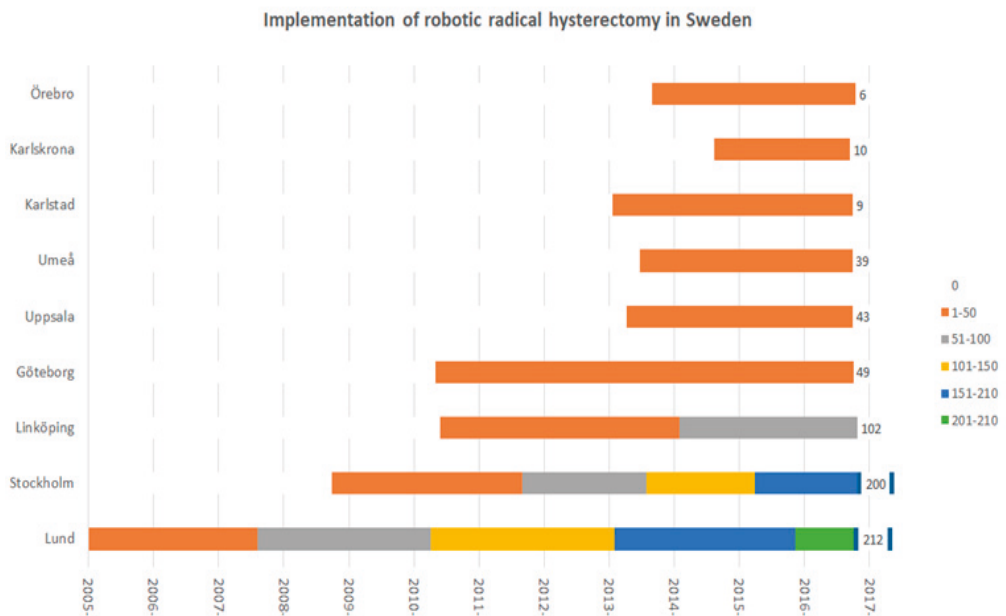


Figure 4. Implementation of RRH in Sweden. (from Study 2 in the present thesis)

### Oncologic outcome

Both surgery and R-CT offers high survival rates in early stages cervical cancer. In Sweden the total 5-year survival rate is 73% and over 90% for early stages (RCC 2021).

### *Radical hysterectomy*

Before 2018 there were no published randomized controlled trials (RCTs) comparing survival rates between the different surgical approaches. The majority of the previously existing retrospective studies showed no difference in survival between RRH and ORH and both Swedish and international guidelines recommended RRH for early stage cervical cancer (RCC 2020, Koh et al. 2015, Cibula et al. 2018).

In 2018 the first RCT; the Laparoscopic Approach to Cervical Cancer (LACC) study comparing minimally invasive surgery (MIS), robotic or laparoscopic, and laparotomy was published. This study included 631 women and showed inferior survival rates for MIS with DFS at 4.5 years of 86.0% compared with 96.5% after ORH. The OS was 99.0% after ORH compared with 93.8% after MIS. In the LACC trial the MIS group 84% were LRH and 16% were RRH (Ramirez et al. 2018). That same year an American register study presented a 4-year OS of 94.7% after ORH and 90.9% after RRH with a median follow-up of 45 months. A decline in the 4-year relative survival rate after adoption of MIS surgery in the US was also seen (Melamed et al. 2018). This led to a change in the treatment guidelines for early stage cervical cancer from MIS to laparotomy (Ramirez et al. 2018).

The results of the LACC-trial have been questioned on several accounts; the lack of internal validity as the surgical proficiency is difficult to assure because not all participating surgeons were subspecialized in gynecologic tumor surgery and since all recurrence were clustered to 14/33 centers. The use of an intrauterine manipulator was not investigated, something that later proved to be an independent risk factor for recurrence in MIS in the SUCCOR trial (Chiva et al. 2020). In the MIS group only 16% (46 women) were treated by RRH and the remaining by LRH, the latter is widely recognized as a very challenging procedure. The Melamed register study was criticized for lacking data and incomplete follow-up. However, several studies published in the last few years presented similar results of inferior survival rates after MIS-RH (Table 3). In subgroup analysis some of these studies found no difference in survival analysis in the subgroup of tumors < 2cm (Table 3).

The SHAPE trial is currently investigating if tumours  $\leq 2$ cm, with low risk of parametrial involvement, can be treated with a simple instead of a RH to reduce intraoperative complication without affecting oncologic outcome (SHAPE 2012). The results from the recently published Concerv trial demonstrate the feasibility of conisation or simple hysterectomy in combination with lymph node assessment in low-risk tumors i.e. tumor size  $\leq 2$  cm, tumor infiltration  $\leq 10$ mm and no LVSI (Schmeler et al. 2021).

**Table 3.** Publications comparing RRH and ORH.

Author Year	Type of study	Recruitment period	Total number of patients	Number of RRH (%RRH of MIS)	DFS RRH or MIS	DFS ORH	RRH cases/center over number of years	Preferred surgical method
Sert 2016	RM	2005-2011	491	259 (100%)	9% recurrence	9% recurrence	259/3/7 years	None
Zanagnolo 2016	RS	2006-2014	307	203 (100%)	8.8% recurrence	10.6 recurrence	307/1/8 years	None
Shah 2017	RM	2001-2012	311	109 (100%)	89.9%	89.1%	109/2/12 years	None
Wallin 2017	RS	2006-2015	304	149 (100%)	13.4% recurrence	10.3% recurrence	149/1/9 years	ORH
Ramirez 2018	RCT	2008-2017	631	50 (16%)	91.2%	97.1%	50/33/9 years	ORH
Melamed 2018	RS	2010-2013	2461	978 (79%)	OS 90.9	OS 94.7	978/357/4 years	ORH **
Alfonzo 2019	RM	2011-2017	864	628 (100%)	84%	85%	628/7/7 years	None
Cusimano 2019	RS	2006-2017	956	52 (11%)	87.9%	89.1%	52/1/11 years	ORH
Doo 2019	RS	2010-2016	105	49 (100%)	24% recurrence	14% recurrence	49/1/7 years	None* /**
Chen 2020	RM	2004-2016	10314	1048 (100%)	94.4%	97.8%	1048/40/13 years	ORH**
Chiva 2020	RM	2013-2014	1272	63 (21.5%)	79%	88.3%	63/126/2 years	ORH
Jensen 2020	RM	2005-2017	1125	595 (94.9%)	91.0*	91.8 vs 91.0***	595/5/12 years	No difference after MIS introduction
Wenzell 2020	RM	2010-2017	1109	369 (73%)	90.2%	89.4%	369/9/8 years	None
Uppal 2020	RM	2010-2017	815	560 (89.3%)	11.5% recurrence	4.4% recurrence	500/9/8 years	ORH

**ORH open radical hysterectomy. MIS minimally invasive surgery. RRH robot assisted radical hysterectomy. RCT randomised controlled trial. RS register study. RM retrospective multicenter. RS retrospective single-center. DFS disease free survival. OS overall survival. NR non reported. \* Better for ORH in  $\geq 2$  cm \*\* No difference in tumors  $< 2$ cm.\*\*\* DFS 91.8 before MIS introduction DFS 91.0 after MIS introduction.**

### Radical trachelectomy

Studies have shown the oncologic safety of RT to be comparable to radical hysterectomy in tumours  $\leq 2$ cm of squamous or adenocarcinoma types (Beiner et al. 2008, van der Velden et al. 2019). Selected cases of stage IA1 with LVSI or a multifocal tumour may also be suitable for RT to increase oncologic safety. Tumours larger than 2 cm carries a higher risk of lymph node involvement or insufficient margins and subsequently of adjuvant treatment and calls for a more restrictive treatment policy (Bentivegna et al. 2016, Van der Velden et al. 2019). In tumours  $>2$  cm, adenosquamous histology has been shown to be an independent riskfactor for recurrence after RT (Li et al. 2019) but not after RH (Bjurberg et al. 2019). RT should not be performed in women with high-risk histology tumours such as neuroendocrine or clear cell tumours (Viswanathan et al. 2004).

A review from 2020 including 2566 women after a RT with a median follow-up of 48 months (range 2–202 months) reported a median recurrence rate of 3.3% (range 0-25%) across studies (Smith et al. 2020). Since ART often is performed in women with tumours larger than 2 cm, comparing individual studies is more suitable between VRT and minimal invasive radical trachelectomy (MI-RT) (Table 5).

The multicenter retrospective IRTA study published in 2021 compared 358 ART with 288 MI-RT where 121 were LRT and 167 RRT. Tumors  $\leq 2$ cm were included but FIGO stage IA1 and women with aborted RT in favor of RH were excluded. The node positivity was 5.3% in the ART group and 4.9% in the MI-RT group. The study found no difference in recurrence rate between ART and MI-RT after 4.5 years (4.5% vs 6.3%). The MI-RT cohort in the IRTA study contains women that are also included in study III-V in this thesis.

**Table 4.** Adapted reproductive and oncologic results presented in recent reviews of radical trachelectomy (Smith et al. 2020, Nezhat et al. 2020, Kuznicki et al. 2021, Bentivegna et al 2016).

Procedure, author	Median F-U time in months	Pregnancy rate %	Preterm delivery rate %	Live birth rate %	Recurrence rate %	Death rate %
VRT Smith et al.	50.9	37.8	33.9	75.1	3.8	1.7
VRT Nezhat et al.	51.5	67.5	34.6	63.4	3.7	NA
VRT Kuznicki et al.	NA	49.9	NA	65.0	4	1.7
VRT Bentivegna et al.	NA	63	21	NA	4	2
MI-RT *Smith et al.	25	9.2	57.1	57.1	0	0
MI-RT Nezhat et al.	26.6	51.5	31.4	56.5	3.3	NA
MI-RT Kuznicki et al.	NA	36.2	NA	57.1	4.2	0.7

NA not available. \* only LRT

## **Fertility outcome following radical trachelectomy**

Pregnancy is feasible after RT. However, even though the procedure is performed to preserve fertility not all succeed in becoming pregnant. Complications that cause infertility such as Asherman's syndrome, ovarian failure and cervical stenosis have been described, especially after an abdominal approach (Egashira et al. 2018). Impaired uterine blood supply following the procedure due to division of the uterine arteries or damage to the blood supply is the possible reason for Ashermans and ovarian failure and might also have a negative effect on following pregnancies and cause uteroplacental insufficiency, intrauterine growth restriction, or preterm delivery (Nezhat et al. 2020, Egashira et al. 2018).

Preterm birth is defined as delivery before gestational week (GW) 37+0. Extremely preterm is defined as GW < 28, very preterm GW 28+0 to 31+6 and moderate or late preterm GW 32+0 to 36+6. Children born prematurely have an increased risk of long-term developmental and neurological disorders as well as mortality. The preterm delivery rate worldwide ranges from 5-13% resulting in 15 million preterm children being born each year. In Europe the rate of preterm delivery is 5-10% (Blencowe et al. 2013). Risk factors for preterm birth include smoking, short cervix, infection, short interpregnancy interval, and a history of preterm birth (Stewart et al. 2010). Second trimester miscarriage, defined as pregnancy loss between GW 14-24 occurs in 1-2% of pregnancies (Wyatt et al. 2005).

The overall etiology of premature birth is multifactorial. Women with a previous RT have an increased risk of second trimester miscarriage and premature delivery. A short post trachelectomy cervical length reduces the cervix innate protective properties against an ascending infection and a remaining cervical length of 10 mm or more is often proposed as a goal during surgery (Alvarez et al. 2018). In pregnancies after RRT, preterm birth is frequently preceded by premature rupture of membranes (PPROM), with an ascending infection as a possible causing factor (Kasuga et al. 2017, Kyrgiou et al. 2017). Bacterial vaginosis (BV) is an imbalance in the vaginal microflora with increased growth of anaerobic bacteria and disappearance of protective lactobacillae (Kairys et al. 2020). It is generally agreed that BV is associated with prematurity and in women with a previous history of preterm delivery the administration of metronidazole can reduce the risk of a following preterm delivery (Dowd et al. 2001, McDonald et al. 1997, Morales et al. 1994, Hauth et al. 1995).

In women with cervical insufficiency a cerclage has been shown to reduce the risk of premature delivery (Owen et al. 2009, Wang et al. 2016). Even though the internal cerclage complicates management of second trimester miscarriages and requires a caesarean delivery its potential preventive effect takes precedence and hence the RRT procedure should include placement of an internal cerclage (Persson et al. 2012). In women with cervical insufficiency alternative prophylactic treatments during pregnancy such as cervical pessary and vaginal progesterone have been



suggested, however the existing evidence is conflicting and cerclage remains the prophylactic intervention of choice in women with a trachelectomy (Dodd et al. 2013, Norman et al. 2016, Goya et al. 2012, Hui et al. 2013).

Several reviews on fertility outcome after RT have been published in the last 5 years (Table 4). Bentivegna et al. included more than 2300 women and found lower fertility rates for ART and LRT (49% and 48% respectively) than after VRT (63%). The fertility rate for RRT, based on few cases, was 81% (Bentivegna et al. 2016). In this study the rate of fetal loss was 21% and the premature delivery rate was 12% after ART (Bentivegna et al. 2016). A review from 2020 including 3000 women similarly reports higher mean pregnancy rates after VRT (67.5%) than after ART (41.9%) and MI-RT (51.5%), but only a few RRT were reported (Nezhat et al. 2020). The preterm delivery rate was 32% and the second trimester miscarriage rate was 5.8% after RT with no difference between surgical approaches (Nezhat et al. 2020). Kuznicki et al. present lower pregnancy rates in MI-RT compared with VRT in their review from 2021 (Kuzmicki et al. 2021) (Table 4). The largest series on pregnancy after RRT published to date reported a term delivery rate ( $GW \geq 36$ ) of 71% (Johansen et al. 2016). The recently published IRTA study did not include reproductive outcome.



**Table 5.** Details from individual studies of radical trachelectomy with different surgical approach.

Study	Number of patient	Median Follow-up time	% FIGO IB1	Tumour size	% LVSI positive	% Aborted fertility	% Metastatic nodes	% Recurrence	DOD	Conception rate % of women trying	2nd trimester miscarriage% of pregnancies > 1st trimester	Live births % of all pregnancies	Premature delivery % of live births
<b>VRT</b>													
Hauerberg et al. 2015	123	56 (5.5-147)	85.8	≤2cm (94.2%)	25	5.6	3.3	5.1% 6/118	1.7% 2/118	76.4% 55/72	3.6% 2/55	68.8% 53/77	22.6% <34GW 12/53
Zusterzeel et al. 2016	132	51 (2-153)	91.7	≤2cm (100%)	32.6	4.5	4.5	6.8% 9/132	3.0% 4/132	57.1% 40/70	0	78.7% 37/47	19% <32 GW 7/37
Plante et al. 2011	140	93 (4-225)	68	≤2cm (89%)	28.6	12.8	10	4.8% 6/125*	1.6% 2/125	44% 55/125	3.8% 3/78	68.9% 73/106	5.2% <32GW 18% <36 GW
Marchioli et al. 2007	118	95 (31-234)	70.3	16.6 ±9.1 <2cm (52.5%)	36.4	12.4	3.4	5.9% 7/118)	1.8% 2/109	NA	NA	NA	NA
<b>ART</b>													
Guo et al. 2019	143	76	-	≤2cm (47.6%)	18.2	37.1	7.1	2.9% 4/143	2.2% 3/139	31.7% 19/60	61.5% 16/26 "midtrimester miscarriage"	30% 10/30	40% 4/10 GW <36
Li et al. 2019	333 of 387	56 (6-169)	76.6	<2cm (60.4%)	18.9	3	3.0	3.3% 11/333	1.5% 5/333	22 unknown of 73.7%	23% 5/22	60.0% 15/25	20% <GW 36
Wethington et al. 2012	101	32		≤2cm (100%)	46.5	30.7	18.8	4%	0% 0/101	28/38	NA	52% 16/31	NA
Nishio et al. 2010	61	27 (1-79)	80.3	≤2cm (80.3%)	50.8%	19.3	14.1	9.8% 6/61	0% 0/61	13.8% 4/29	0	100% 4/4	50% <32 GW
<b>MI-RT</b>													
Ebisawa et al. 2013	56	60 (4-138)	92.9	-	25.0%	5.4	0	1.9% 1/53	1.9% 1/53	52.0% 13/25	12.5% 2/16	61.9% 13/21	15.4% <32GW 53.8% <36GW
Park et al. 2014 LRT	88	44 (3-105)	91.1	≤2cm (59.7%)	18.8	10.2	3.8	11.4% 9/79	1.3% 1/79	16.5% 13/79	-	76.5% 13/17	54% <36 GW

## Postoperative complications

Postoperative complications are often reported using the Clavien Dindo classifications system (Clavien et al. 2009). It covers complications arising within 30 days post surgery but does not include intraoperative complications (Table 6). This nomenclature for surgical complications is not ideal as some complications might be difficult to define as either intraoperative or postoperative. A complication can be discovered during surgery (i.e. intraoperative) or arise during surgery but be discovered after surgery (i.e. postoperative) or arise after surgery (i.e. also postoperative). Another way of classification would be to combine the first two categories into complications directly associated with surgery.

**Table 6.** Clavien Dindo classification system.

Grade	Definition
1	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.
2	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
3	Requiring surgical, endoscopic or radiological intervention
3a	intervention not under general anesthesia
3b	intervention under general anesthesia
4	Life-threatening complication (including CNS complications)‡ requiring IC/ICU-management
4a	single organ dysfunction (including dialysis)
4b	multi organ dysfunction
5	Death of a patient

Short term postoperative complication rates 4-6 weeks after RH range between 5-16% depending on surgical modality and definition. The most common are bladder dysfunction, lymphocyst formation and infection followed by deep venous thrombosis and pulmonary embolism. Intraoperative complications include injury to the urinary tract, vessel injury and injury to the genitofemoral or obturator nerves (Manchana et al 2009, Boggess et al 2008).

Long-term complications such as voiding dysfunction, lymph cyst, and lymphedema can affect the woman long-term (Wallin et al. 2016, Manchana et al 2009). The highest morbidity is found in women where primary surgery is followed by RC-T (Landoni et al. 1997).

## Quality of Life after RRT

A cancer diagnosis has major physical, psychological and social impact on patients and their families. Many women are young when diagnosed and treated for cervical cancer with a long life ahead where side effects may affect their quality of life. In

patients of reproductive age, an additional concern is the effect of diagnosis and treatment on their future fertility.

The European Organization for Research and Treatment of Cancer (EORTC) developed the EORTC-C30 in 1987 as an instrument to investigate quality of life in clinical trials in oncology. It was first created for lung, breast and esophagus cancer and its reliability and validity have been established (Aaronson et al. 1993). The refined version used today is the EORTC QLQ-C30 3.0. The cervical cancer module of QLQ-CX24 is a supplementary questionnaire where validity and reliability also have been established (Greimel et al. 2006). The LYMQOL was originally developed and validated in 2010 (Keeley et al. in 2010). The Swedish version of LYMFQOL was evaluated in 2020 and the results of the LYMFQOL was significantly associated with perceived lymphedema and the questionnaire demonstrated good reliability (Wedin et al. 2020).

Quality of life (QoL) after radical hysterectomy have been addressed in several studies (Bjelic-Radisic et al. 2012, Frumovitz et al. 2005, Jensen et al. 2004) where the women report decreased sexual functioning and lower emotional functioning after RH. Quality of life in women after radical trachelectomy has been less extensively studied. Reports suggest reduced QoL, urogenital morbidity, lymphedema and sexual dysfunction (Flemming et al. 2016, Froeding et al. 2016, Chan et al. 2015). QoL studied in women with a longer follow-up time after RT suggest some improvement with time (Malmsten et al. 2018). QoL is more affected in women where oncologic treatment is added to the surgical treatment (Jensen et al. 2004, Bjelic-Radisic et al. 2012).



# Aims

## General aims

The overall aims of this research project were to evaluate long term oncologic and reproductive outcome as well as complications and quality of life after robot assisted surgery for early stage cervical cancer.

## Specific aims

### Study I

- To compare disease free survival and overall survival after open radical hysterectomy and robot-assisted radical hysterectomy for early stage cervical cancer in Sweden.

### Study II

- To investigate the effect of increased surgical experience, per institution on recurrence rate and pattern of recurrence after robot-assisted radical hysterectomy.
- To investigate the effect of increased surgical experience, per institution on the rate of intraoperative and postoperative complications after robot-assisted radical hysterectomy.

### Study III

- To evaluate long-term oncologic outcome, reproductive outcome and postoperative complications following fertility sparing robot-assisted trachelectomy.

### Study IV

- To evaluate if a metronidazole/no sexual intercourse regime can prevent premature delivery in women after fertility sparing robot-assisted trachelectomy.

### Study V

- To evaluate quality of life, sexual function, lymphoedema and other long-term clinical outcomes after fertility sparing robot-assisted trachelectomy in a single institution setting.

# Material and methods

## Study 1

The management of cervical cancer in Sweden is centralised to seven university hospitals where the absolute majority of women receive their treatment. It is compulsory for both pathologists and clinicians to report newly detected cancers to the National Cancer Register (NCR) in Sweden. In NCR, the coverage of malignant tumors is greater than 95% of which 99% have been histologically verified (Barlow et al. 1998). The Swedish Quality Register of Gynecologic Cancer (SQRGC) was established in 2008 and since 2011 cervical cancer is included in the register. This is a nationwide, online register where data on patient and tumor characteristics, details on received surgical and oncological treatments, outcomes, and follow-up data is prospectively entered. Information on individuals can be accessed using the personal identification number assigned to each individual in Sweden. The SQRGC is linked to the NCR and the National Death Registry to ensure control of coverage and lifelong follow-up of patients. The SQRGC data have been independently validated for ovarian and endometrial cancer (Rosenberg et al. 2018).

In this study the SQRGC was used to identify all women  $\geq 18$  years with FIGO stage IA1-IB1 cervical cancers of squamous, adenocarcinoma or adenosquamous histological subtypes having a primary radical hysterectomy (RH) according to Querleu Morrow classification type B or C performed in Sweden between January 2011 and December 2017. The inclusion period started in 2011 since cervical cancer was included in the SQRGC that year. To identify women not yet entered in the SQRGC we used local hospital registers to identify any remaining women eligible for inclusion. After identification, a full chart review was done on all women where patient and tumor characteristics including surgical approach, complications, need of adjuvant therapy and recurrence were recorded. The follow-up continued until October 24, 2018 or death. In the study period 2011-2017 the selection of surgical approach was largely based on the accessibility of the robotic system. We excluded women with high risk histology, RH in conjunction with a caesarean section or intraoperative findings that led to abortion of the RH.

For statistical analysis of continuous variables, the Student's t-test was used, while categorical variables, depending on category size, were evaluated using Pearson's chi-squared test or Fisher's exact. Overall survival (OS) and disease-free survival (DFS) were estimated using the Kaplan Meier approach (Kaplan et al. 1958).

Proportional hazards model was used to estimate hazard ratios for each of the variables: age, tumour size, lymph-vascular space invasion (LVSI), grade, lymph node status and primary treatment. Propensity score matching (Rosenbaum et al. 1983) was used to match individuals in age, tumor size, LVSI, grade, lymph node status, primary treatment and year of diagnosis to reduce the risk of bias in the estimate of the difference in survival for open and robotic radical hysterectomies. To estimate the difference in survival between the surgical approaches, a proportional hazard model in matched data was used (Breslow et al. 1975). A *p*-value less than 0.05 was considered significant and in all cases the R statistical software version 3.5.1 was used.

## Study II

In this study all RRH performed in Sweden from the implementation in December 2005 until June 2017 were included. This was to guarantee a minimum 24-month follow-up. In this study squamous, adenocarcinoma or adenosquamous histology was included and preoperative stage IA2-IB1 (FIGO 2009). Women with FIGO stage IA1 from study I was not included. The more historical RRH, i.e., performed before 2011, were identified using local hospital registers since the SQRGC did not include cervical cancer prior to 2011. The RRHs were Querleu–Morrow classification types B2 or C1 (Querleu et al. 2008). A complete full chart review on all women was done using common criteria for patients, tumor characteristics and follow-up data including intraoperative and postoperative complications and recurrence within 24 months. Operations were chronologically numbered per institution. Since tumor size was defined as the largest diameter in the final pathology report after hysterectomy or cone biopsy specimens, it represents a minimum size of the tumor. Women with large tumors (> 4 cm at final pathology), positive lymph nodes or women with insufficient margins (<5mm) were recommended adjuvant radio chemotherapy (RC-T). The criteria for offering adjuvant RC-T remained unchanged during the observation time. Complications diagnosed and treated during primary surgery (intraoperative) or directly related to surgery but diagnosed postoperatively were combined to “complications directly associated with surgery” in the analysis. Postoperative complications using the Clavien–Dindo classification up to 30 days post-surgery were also separately registered (Clavien et al. 2009).

Oncologic outcome was registered at 24 months and defined by the date of histologic verification by biopsy for women with recurrence. As health care for cervical cancer is only provided by public hospitals in Sweden, loss to follow-up only occurs in case of emigration. This occurred in one woman who was consequently excluded from the 24 months analysis. Intraoperative abortion of the RRH in favor of RC-T or women who refused recommended adjuvant treatment



were also excluded. The recurrences were grouped into four categories to enable the analysis of pattern of recurrence: locoregional, abdominal, lymph nodes/distant and multiple. The hypothesis that surgical experience would have an impact on oncologic outcome might be influenced by whether adjuvant RC-T was administered and for this reason, the data set was split into two subgroups and analyzed accordingly.

Since the introduction of RRH differed in time across hospitals and different baseline surgical and robotic skills might influence the result, institutional recurrence rate depending on time of introduction was also investigated.

In logistic regression whether the probability of recurrence within 24 months were influenced by patient's age, tumor size, histology, center of treatment or surgical order was tested. These results were then tested against the null hypothesis of an unimproved recurrence rate over time. If an effect of learning exists, it might diminish over time and to compensate for this a logistic regression model was constructed. To compensate for a possible difference in surgical skills between the hospitals the logistic regression model was applied for all six included hospitals but also for the three hospitals with the highest number of performed RRHs (>100) and the earliest implementation. A model was constructed to identify a possible cut off level for comparison of recurrence rates between the two groups (introductory and experienced) over time in tumors of median size. After this the chi<sup>2</sup> test was used to compare recurrences between the two groups and to investigate possible skewness between the groups. The data were analyzed using the Python package Statsmodel Discrete Logic (version 0.11.1, Texas, USA) or the SPSS version 12.0 statistical software was used (SPSS, Chicago, IL, USA) and a *p*-value of less than 0.05 was considered significant in all statistical tests.

## Study III-IV

Fertility sparing radical trachelectomy is a rare procedure. Robot-assisted trachelectomy (RRT) is performed at a restricted number of centres and in Sweden only two university hospitals can present long term results after RRT. To enable analysis of a larger cohort of RRTs a multinational cooperation was established in 2019. In this study all consecutive women planned for RRT at Skåne University Hospital, Sweden (SUH), Karolinska University Hospital, Sweden (KUH), UNC Medical Centre Chapel Hill, the US (UNC), Severance Hospital of the Yonsei University, South Korea (YUHS) and Royal Surrey County Hospital, the United Kingdom (RSCH) between December 2007 and September 2019 were included. (**Study IV** only includes women from KUH, SUH, YUHS and RSCH.) Women with a FIGO 2009 clinical stage IA2 and stage IB1 cervical cancer in whom a RRT was attempted were included. Women with FIGO stage IA1 were required to have

evidence of lymph vascular space invasion (LVSI), multifocal disease, adenosquamous histology or a cone biopsy with positive margins to be included. Chart reviews were performed by six of the authors. In study III women offered an RRT outside guidelines (i.e. tumors > 2 cm and high risk histology) were not included.

A uterine artery preserving RRT was performed (Persson et al. 2008, Persson et al. 2012). The majority of RRTs was performed by one surgeon at each centre. A cervical cerclage was placed medial to the ascending uterine artery at the level of the uterine isthmus using a permanent monofilament (Prolene®, Nylon®, Ethilon®) or multifilament suture (Ethibond® or Gore-Tex®).

The use and practice of sentinel lymph node (SLN) biopsy differed among sites during the study period. At SUH, SLN biopsy was used in all patients and at KUH in a majority of cases, using indocyanine green as tracer in the majority of cases. In the remaining 3 hospitals the use of SLN biopsy was scarce. The main indication for applying a SLN technique at SUH and KUH was to achieve intraoperative information on lymph node metastases to tailor further lymphadenectomy and to transpose the ovaries when the procedure was aborted in favour of upfront radio chemotherapy (RC-T). As a rule, the proximal margin of the trachelectomy specimen was sent for frozen section.

The fertility sparing attempt was aborted during or after surgery in case of metastatic lymph nodes, insufficient margins or, in one patient, met Sedlis criteria. In case of insufficient (<5mm) proximal cervical margins on final pathology a rescue hysterectomy was performed. In case of positive lymph nodes and/or any other insufficient margins (<5mm) RC-T was administered.

The Clavien Dindo (CD) scale was used to grade postoperative complications (Clavien et al. 2009). Follow-up was performed at least twice annually for a minimum of five years. All recurrences were histologically verified, defined by date of verification and location. Long-term complications such as cerclage erosion and cervical stenosis /hematometra were recorded. Lymphedema was not consistently reported and hence not analyzed. Reproductive and obstetric outcomes were recorded.

For regression analysis of factors associated with fertility, data from all women with an active attempt to conceive  $\geq 6$  or 12 months (study IV and study III respectively) excluding women with a previous history of fertility problems was assessed. Postoperative non-pregnant cervical length was routinely controlled by vaginal ultrasonography ( $n=79$ ) or MRI ( $n=17$ ) at three of the institutions. In one institution a regime of oral metronidazole 400 mg x2 was prescribed from gestational week (GW) 15+0 to 21+6 and women were advised to abstain from sexual intercourse from instigation of the metronidazole treatment and throughout the pregnancy.

For analyses of factors associated with second trimester miscarriages and premature deliveries pregnancies beyond first trimester were included, excluding premature caesareans due to obstetric complications such as preeclampsia/ HELLP syndrome and placenta previa and excluding women in whom a cerclage was not placed or had been removed. All women were planned for caesarean delivery at gestational week 36 to 38 to deliver the baby before onset of labour.

Statistical analyses: We used Mann Whitney to compare continuous variables and Pearson's Chi<sup>2</sup>-test for categorical variables. Regression analyses were performed when appropriate. The data was entered into a Microsoft Excel database, pseudo-anonymized and analyzed using SPSS version 12.0 statistical software (SPSS, Chicago, IL, USA). A *p*-value of less than 0.05 was considered significant in all statistical tests.

## Study V

In this single institution study consecutive women undergoing robotic radical trachelectomy (RRT) between December 2007 and November 2020 at Department of Obstetrics and Gynecology, Skåne University Hospital, Lund, for cervical cancer FIGO (2009) stage 1A1-IIA were included. Women with FIGO stage IA1 were only included if they had lymph vascular space invasion (LVSI), multifocal disease or a cone biopsy with positive margins. Prior to the RRT a vaginal ultrasonography, a pelvic MRI, a CT-scan and a clinical examination under anaesthesia for staging purposes were performed. Sentinel lymph node (SLN) biopsy was performed in all women initially using radiotracer (29%) and later Indocyanine Green (71%) and sent for frozen section followed by the trachelectomy specimen. After SLN removal a full pelvic lymphadenectomy was performed except in women with stage 1A1 cancer. The RRT was aborted in case of metastatic SLN or insufficient proximal margins at frozen section. If the RRT was completed as planned an internal cervical cerclage was placed. A rescue hysterectomy was performed in case of insufficient proximal cervical margins and adjuvant radio chemotherapy (RC-T) was recommended in case of positive lymph nodes or insufficient margins.

Three validated questionnaires, QLQ-C30 and QLQ-CX24 found at eortc.org and LYMQOL validated for Swedish patients in 2020 (Wedin et al. 2020), study information and a written consent form were sent to all women in a pre-paid return envelope in April 2021 and resent to non-responders after four weeks. The QLQ-C30 questionnaire evaluating global health status (GHS), functioning scales, symptom scales and single-item symptom scales after cancer treatment in a multicultural, multidisciplinary setting (Aaronson et al. 1993). The QLQ-CX24 is a disease and treatment-specific questionnaire for patients with cervical cancer evaluating four functioning scales and five symptom scales. (Greimel et al. 2006).

The scoring manual of EORTC was used to transform all scale and item scores to a 0–100 scale where a high GHS score represents a high QoL, a high score on functioning scales represent healthy levels of functioning but a high score on symptom scales represents high levels of problems (Fayers et al. 2001). The first three domains of the LYMQOL were used: function, body image and symptoms. The total score for each domain of the LYMQOL was calculated for each domain with range 0-4 (Wedin et al. 2020). For each domain a high score represents a large impact of the lymphoedema on that domain.

Clinical follow-up was performed at four months interval for the first two years, thereafter at every six months. The Clavien Dindo scale was used to grade postoperative complications (Dindo et al. 2004). Recurrences were defined by date of histological verification and location. Women who conceived had a scheduled visit at GW 10 for counselling and planning. Starting in 2008, the regime with oral metronidazole described in Study IV was applied. Caesareans performed as planned at GW  $\geq 36+0$  were considered full term.

## Ethical considerations

Study I: The ethical review board at Gothenburg University (DNR 397-18) approved the study. Patient consent is obtained for registration in the SQRGC.

Study II: The institutional review boards at Lund University (DNR 2008-663), the Karolinska Institute (DNR 2015-2140) and Gothenburg University (DNR 397-18) approved this study. Patient consent is obtained for registration in the SQRGC.

Study III-IV: The study was approved by the Institutional Review Boards at Lund University (DNR 2008-663, DNR 2018-749), the Swedish national Review board (DNR 2020-06968), Karolinska Institute (DNR 2015-2140), University of North Carolina (IRB 19-2154), Yonsei University Health System (4-2019-1274) and Clinical Audit Group approval at Royal Surrey NHS Foundation Trust. All women gave their informed consent to robot-assisted approach.

Study V: The study was approved by the Institutional Review Boards at Lund University (DNR 2008-663, DNR 2018-749) and the Swedish national Review board (DNR 2020-06968). All women gave their informed consent to robot-assisted approach.

# Results

## Study I

Of 864 included women 628 (73%) underwent RRH and 236 (27%) ORH. A difference was seen in tumor size ( $p < 0.020$ ) and LVSI ( $p < 0.001$ ). This led to a difference in adjuvant treatment between groups, where 32.3% of ORH received adjuvant treatment and 20.9% of RRH. There was no difference in number of metastatic nodes. 94% of the surgeries were performed at a tertiary center.

The median follow-up times were 55.7 months after ORH and 44.5 months after RRH ( $p < 0.001$ ). During this time 84 (9.7%) of the women were diagnosed with a recurrence, with no difference between the groups ( $p = 0.119$ ). There was no difference in site of recurrence between the groups however, vaginal metastases seemed more frequent after RRH (35.8% vs 27.7%  $p = 0.269$ ) and port-site metastases were exclusive to the RRH group.

There was no difference in the 5-year OS with 92% (95% CI, 88-96) after ORH and 94% (95% CI, 91-96) after RRH. After the OS was adjusted for tumor size or stratified into surgery alone or surgery in combination with adjuvant therapy, the OS rate remained similar between the groups.

There was no difference in the 5-year DFS with 84% (95% CI, 79-90) in the open group and 88% (95% CI, 85-91) in the robotic group. After the DFS was adjusted for tumor size or stratified into surgery alone or surgery in combination with adjuvant therapy, the DFS rate did not differ between the groups. Altogether, 84 women were diagnosed with a recurrence (9.7%) and 38 recurrences were registered among the total of 49 deaths.

In the propensity score analysis, 232 women were matched according to criteria mentioned in the methods. After this matching there was also no difference in BMI, FIGO stage or histology between the groups. The survival analysis between these matched groups showed no difference in OS (92% in both group) or DFS (85% in the open and 84% in the robotic cohort).

In the univariable analysis with DFS as the end-point, tumor size, grade, LVSI, lymph node metastasis and adjuvant treatment were all associated with poorer prognosis. However, in the multivariable analysis only tumor size ( $p < 0.001$ ) and grade 3 ( $p = 0.02$ ) were found as independent risk factors. In the univariable analysis

with OS as the end-point, tumor size, grade, LVSI, lymph node metastasis and adjuvant treatment were all associated with poorer prognosis. No such association remained in the multivariable analysis.

## Study II

During the study period, nine institutions performed RRH. The aim of this study was to evaluate the effect of increased surgical experience, per institution, hence the three institutions that performed ten or fewer RRH were deemed unsuitable for this analysis. Of the remaining, three hospitals performed >100 RRH and three hospitals <50. Sixty women were excluded due to a high-risk histology, FIGO 2009 stage <1A2 or >1B1, intraoperative abortion of the RRH in favor of RC-T, an unwillingness to receive recommended adjuvant treatment or lost to follow-up due to emigration ( $n=6$ ).

In the final analysis 489 women who received only surgical treatment and 146 women with surgical and adjuvant treatment, due to lymph node metastasis, large tumors or insufficient margins remained.

A decrease in the rate of recurrence with increased experience in women without RC-T was seen in the regression analysis. This was shown for all six hospitals as well as for the three hospitals with most experience (>100 RRHs). To find a possible inflection point a statistical model using the three most experienced hospitals indicated that probability of recurrence decreased with increased experience with a cut-off at approximately 50 procedures. Hence, the first 50 RRH (introductory cohort) from each of the six hospitals were compared with the remaining >50 RRH (experienced cohort) from the most experienced hospitals.

When comparing the introductory cohort and the experienced cohort in the group of women that had only surgical treatment, fewer recurrences were noted in the experienced cohort than in the introductory cohort (3.6% vs 9.3%,  $p = 0.009$ ). Fewer recurrences were also seen in the experienced cohort in tumors <2 cm in women with only surgical treatment ( $n = 373$ , 1.9% vs 7.0%,  $p = 0.01$ ) and in tumors <2cm in all women regardless of adjuvant treatment ( $n = 43$ , 2.9% vs 7.9%,  $p = 0.02$ ).

This decline in rate of recurrence with gained experience was not seen in tumors  $\geq 2$ cm or women who received adjuvant RC-T regardless of tumor size.

Three of the 635 women needed a conversion to laparotomy due to adhesions, vessel injury or subcutaneous emphysema. Ten women experienced an intraoperative complication. Severe postoperative complications, CD  $\geq$ IIIa occurred in 4.1%. (Clavien et al. 2009). The rate of severe postoperative complications decreased with increased experience (2.5% vs. 6.1%,  $p = 0.03$ ). When the postoperatively diagnosed complications directly associated to surgery, i.e., ureter injury,

vesicovaginal fistulas and compartment syndrome were added to the intraoperative complications group a significant decrease in complications was seen with increased experience ( $p = 0.01$ ).

## Study III

In this study 166 women were planned for RRT according to guidelines (i.e. tumors  $\leq 2$  cm and squamous, adenocarcinoma or adenosquamous histology). In 17 women (10%) the fertility sparing attempt was aborted due to lymph node metastases ( $n=8$ , 5%) or insufficient margins ( $n=8$ , 5%) or Sedlis criteria diagnosed during or after surgery ( $n=1$ ). 12 women (7.2%) recurred, and the most common site was a lateral pelvic recurrence. Of the 149 women in whom the RRT was completed, nine (6.0%) recurred. Median follow-up time was 58 months. Two women died of the disease at 8 and 45 months after surgery. 135 of the 149 women with a completed RRT had follow-up data for  $\geq 12$  months and no recurrence was noted. 88/135 women (65%) actively tried to conceive where 80% ( $n=70$ ) became pregnant. This resulted in 103 pregnancies and 76 live births. The prematurity rate was calculated based on pregnancies beyond the first trimester excluding first trimester miscarriages ( $n=19$ ) and ongoing pregnancies ( $n=3$ ). A second trimester miscarriage ( $n=5$ ) or a preterm caesarean section ( $n=22$ ) were seen in 27/81 (33%) of pregnancies who developed beyond the first trimester. Four preterm caesarean section were believed to be unrelated to RRT (three Preeclampsia/HELLP and one placenta previa). 86 % of pregnancies beyond the first trimester were delivered at gestational week  $\geq 32+0$ . In women with preserved fertility 35% (47/135) did not try to conceive. The baby take home rate was 72 % among women trying to conceive and 38% in all 166 women planned for RRT, i.e. according to intention to treat analysis. There was no association between premature birth and cervical length, preservation of the uterine artery (preserved in all but five women) or type of cerclage ( $p=NS$ ). The proportion of premature deliveries after RRT compared to Swedish population-based data can be seen in Table 7.

**Table 7.** Gestational age at delivery following RRT. Number of preterm deliveries ( $n=22^*$ ) and deliveries  $\geq 36$  weeks out of total number of complete pregnancies ( $n=70$ ) after RRT compared to Swedish population-based data of pregnancies with live births 2018  $n=104686$ .

	Extremely preterm <28+0	Very preterm 28+0 to 31+6	Early preterm 32+0 to 33+6	Late preterm 34+0 to 35+6	Term >36+0	Total
<b>Deliveries after RRT*</b>	3 (3.9%)	4 (5.2%)	1 (1.3%)	14 (18.4%)	54 (71.0%)	76
<b>Deliveries in Sweden 2018**</b>	267 (0.3%)	508 (0.5%)	687 (0.7%)	1775 (1.7%)	101449 (96.8%)	104686

\* Includes preterm deliveries due to preeclampsia and HELLP syndrome. \*\*The Swedish Pregnancy Register. Statistics from year 2018, courtesy of Dr Andreas Herbst.



Of the 149 women with a completed RRT, two intraoperative complications (bladder injury sutured during surgery and compartment syndrome of the leg) were noted. 36 (24%) experienced an early postoperative complication according to the Clavien Dindo classification. More than 70% were mild to moderate whereas 10 women (7%) had a complication that required intervention, where pelvic lymph seroma, pelvic hematoma or vaginal bleeding were the most common. Lymphedema was not consistently reported and therefore not analyzed. Four women required a secondary hysterectomy (due to menorrhagia  $n=2$ , cervical stenosis  $n=1$  and persistent dysplasia  $n=1$ ) two of these women had given birth prior to the secondary hysterectomy. Cervical stenosis was divided into “internal” (narrowing of the inner cervix with a risk for hematometra) or “external” (narrowing of the external os due to epithelialization) or a combination thereof. Three women had an internal or of combined type and 15 an external, in total 14% of the 125 women with complete data on stenosis. Cervical stenosis was not associated with inability to conceive but 2/3 women with internal stenosis and 4/15 with external stenosis did not attempt pregnancy. In women with a Gore-Tex® cerclage 5/25 had an rejection /erosion of the cerclage to the vagina which was not seen in women with Prolene® or Ethibond® cerclages ( $p<0.01$ ).

## Study IV

Median age of the 129 women with a completed RRT was 31 years, (range 23-41) Thirty-two women (24.8%) had given birth prior to the RRT.

The median follow-up time was 50 months (range 2-140 months) in the 109 women remaining in the reproductive analyses after excluding women with a recurrence prior to pregnancy ( $n=8$ ), secondary hysterectomies ( $n=2$ ) and women with less than six months follow up ( $n=10$ ). 52 (73.2%) of the 71 women with an active wish to conceive became pregnant.

56 pregnancies were recorded, 3 were not included in the analysis of prematurity due to preeclampsia/HELLP syndrome and placenta previa which necessitated premature deliveries not related to the previously performed RRT. In the 22 women where a metronidazole/no sexual intercourse regimen was applied 2 (9%) had a premature delivery compared to 13/31 (42%) of women that were not prescribed the regime ( $p = 0.009$ ). The statistical difference remained even after regression analyses including other possible contributing factors were performed ( $p = 0.001$ ). There was no second trimester miscarriage or premature delivery  $GW < 28+0$  in the metronidazole regime group compared with 16% (5/31) in women who were not prescribed the regime. Neither parity prior to RRT, preservation of the uterine artery, post trachelectomy non-pregnant cervical length nor type of suture



(monofilament compared with multifilament) used for the cerclage was associated with the risk of premature delivery at univariate analysis. Five women received vaginal progesterone in the cohort without the regime resulting in 1 premature delivery at GW 29 + 0 due to chorioamnionitis and 4 term caesareans. When they were excluded there was a four-fold reduction of second trimester miscarriage and premature delivery when the metronidazole regime was applied (9% vs 46%,  $p = 0.005$ ). Data on postoperative non-pregnant cervical length was available in 96 (74.4%) women. An inability to conceive was associated with a shorter post trachelectomy non pregnant cervical length at univariate analysis but without a distinct cut-off level ( $p = 0.04$ ).

## Study V

In seven of the 49 women planned for RRT the concept was aborted due to metastatic SLN at frozen section ( $n=3$ ), intraoperative insufficient margins ( $n=1$ ) or insufficient margins on final pathology ( $n=3$ ). With no woman lost to follow-up the median follow-up time was 54 months (range 9-124 months).

One woman with an aborted RRT recurred with an ovarian metastasis at 36 months, but none of the women with a completed RRT recurred. In women with a completed RRT 67% tried to conceive with a 79% success rate resulting in 39 pregnancies. All pregnancies beyond the first trimester resulted in live babies. Hence there were no second trimester miscarriage. 24 pregnancies were delivered at term and 4 prematurely. The metronidazole/no sexual intercourse regime described in study IV was applied in 26 of 28 pregnancies and in that cohort 92% were delivered at GW  $\geq 36+0$ . There were no intraoperative complications and no severe ( $CD \geq$  grade III) postoperative complications. Mild to moderate postoperative complications were seen in nine women (18%). Cervical stenosis was seen in three women; one internal who suffered from infertility and two external who were asymptomatic. There was no cerclage erosion to the vagina. Cerclage erosions to the cervical stroma occurred in two women admitted for uterine contractions before their planned Cesarean, in one of these a cerclage replacement was necessary, and that woman later had a second term delivery.

Thirty-three (79%) of the 42 women with a completed RRT answered the questionnaires at a median of 85 months (range 6-158) after surgery. The QLQ-C30 questionnaire was complete while five answers on sexual/vaginal functioning was missing in the QLQ-CX24 and two on Body Image and Symptoms respectively in the LYMQOL. The results from the QLQ-C30 showed a median global health status (GHS) score of 75, emotional functioning had a median score of 83.3 whereas physical, role, cognitive and social functioning had a median score of 100. In the symptom scale fatigue scored the highest (median 11.1, mean 17.2) and on the single

item scales all parameters had a median score of 0. In the disease specific QLQ-C24 questionnaire sexual/vaginal functioning had the highest median score of 25, followed by body image at 11.1. Symptom experience had a median score of 9.1 (mean 11.5) whereas lymphedema, peripheral neuropathy, menopausal symptoms and sexual worry had a median score of 0. Sixteen women (48%) did however report some worry that sex would cause physical pain. The functional items sexual activity and sexual enjoyment both had a median score of 66.7. Fifteen of the 33 responders (45%) reported symptoms of lymphedema, nine (27%) bilaterally and six (18%) unilaterally. Three women (9%) rated their symptom as severe. Fourteen women reported that the lymphedema affected their body image to some extent and the mean score on how much the lower limb swelling affected the woman's function, body image and gave symptoms showed a mean of 1.38, 1.71 and 1.6 respectively where each area can have scores ranging from 0-4.

# Discussion

## Study I-II

Prior to 2018 several retrospective studies supported the oncological safety of minimal invasive RH (Hoogendam et al. 2014, Sert et al. 2011, Sert et al 2016, Zanagnolo et al. 2016). In endometrial cancer 2 RCTs demonstrated similar survival rates and superior outcome in terms of short term complications and length of stay after MIS compared to open surgery (Walker et al. 2009, Janda et al. 2017). The surprising results from the randomized controlled LACC-study and an American register study by Melamed et al. with inferior survival rates after minimally invasive surgery (MIS) compared to ORH, changed the treatment guidelines for early stage cervical cancer from MIS to laparotomy (Ramirez et al. 2018, Melamed et al. 2018). Questions were raised regarding surgical proficiency, the use of uterine manipulator and the low rate of robotic procedures in the LACC study and the lack of data and incomplete follow-up in the Melamed study. However, several recent studies have presented similar results of inferior survival rates after minimal invasive radical hysterectomy, although some found no difference in tumours <2cm (Table 3). Although affecting the same organ, the more superficial growth and increased exposure of cervical cancers as well as the younger age at diagnosis and a more complex surgical procedure might explain the difference between outcome in women with cervical and endometrial cancer.

Study I, a national study of prospectively retrieved quality register data with retrospective control of 628 robot-assisted radical hysterectomies (RRH) over a period of 7 years found no survival difference between RRH and the 236 ORH. Factors associated with the similar oncologic results after ORH and RRH in study I could be; the highly centralised treatment for gynecologic cancer in Sweden to seven university clinics with gynecologists subspecialised in tumor surgery, strict adherence to national guidelines when selecting patients for surgery or adjuvant RC-T, avoiding use of an intrauterine manipulator and complete follow-up due to the compulsory reporting of recurrence to a national data base. A study from Denmark with a similar centralised cancer treatment as in Sweden showed similar results with no difference in oncological outcome between RRH and ORH (Jensen et al. 2020). A previous Swedish study found improved survival following centralisation of care for ovarian cancer surgery (Dahm-Kähler et al. 2016).

An important aspect when investigating a new surgical method is the effect of increased experience. Study I included patients from seven university hospitals where the two major contributing hospitals had passed their learning phase of RRH. A clinical threshold in a learning curve does not occur after an exact number of procedures nor is it when the surgeon reaches a plateau. A threshold should be a phase of high-quality performance. Studies have shown that increased experience reduce surgical time, blood loss and postoperative complications in RRH (Wallin et al. 2017, Yim et al. 2013, Cao et al. 2015, Lenihan et al. 2008, Lonnerfors et al. 2015). The results from study II indicate that increased experience per institution resulted in a decreased rate of recurrence. This was shown in women who did not receive adjuvant RC-T as well as in women with tumors < 2 cm, regardless of given adjuvant treatment. In women with tumors  $\geq$  2 cm or women who received adjuvant RC-T there was no difference, possibly due to risk of occult disease at time of surgery and prevention of locoregional recurrences by the RC-T. Two single-institution studies published in 2020 investigated the impact of learning curve on oncological outcome after RRHs and found improved survival rates with increased surgical experience, achieving similar levels of adequate experience as in study II (Baeten et al. 2020, Eoh et al. 2020). Although more difficult to measure, learning curve includes the surgeons individual learning curve and the institutional learning curve. An adequate caseload per centre is necessary to achieve a plateau for both the surgeon and team. This is particularly important for a relatively rare procedure such as a RH. The Melamed study presented data from 479 institution with 357 institutions performing 978 RRH during a 4 year study period (personal communication Dr Melamed) which also represented the introductory phase of robot-assisted surgery in the US. In Table 3, RRH cases/institution/year is presented for comparison and the average annual case load in the Melamed study was 0.68 RRH per institution. Although the number of RRHs per institution per year in study II were only 7-23 in 2017 the two major hospital that contributed with 65% of cases had an annual caseload of 23-31 RRH during 2015-2017. Another important aspect to consider when examining a learning phase is the transfer of knowledge and experience from surgeons experienced in RRH during the introductory phase in both their own and in new hospitals that would be expected to improve their baseline skills. This was implied in study II when comparing early cohorts from the hospitals where RRH was firstly implemented to the two hospitals with the latest introduction. In Sweden, the hospitals with later implementations were aided by proctoring by surgeons from either of the two institutions with the earliest start.

In summary, study I and II suggest that RRH is oncologic safe if performed in a centralized setting at an institution with experience in RRH and with a continuous high case-load of robotic surgery as well as RRH. Important preventive measures are avoiding the use of an intrauterine manipulator, to be careful when manipulating lymph nodes during lymphadenectomy and in case of an exophytic tumour consider conization at the onset of surgery. This was evident in the Succor Cone study that present a 65% reduction in the risk of relapse in women with a cervical conization

prior to RH compared to women without cervical conization. This effect was most evident in tumors 2-4 cm and in women with minimally invasive surgery (Chacon et al. 2020). It is important to consider overall organization of care, caseload and the timing of a study in relation to the implementation of a new technique, when comparing a new to a well-established surgical method.

## **Methodological considerations study I-II**

Population-based register studies, such as study I and II in this thesis often present a large study sample and long follow-up which reduces random errors. In study I and II, the SQRGC was used in combination with local hospital records to include all eligible patients and hence reduce information bias. The SQRGC is linked to the NCR and the National Death Registry and have been independently validated for ovarian and endometrial cancer (Rosenberg et al. 2018). Study I and II can be seen as hybrids between prospectively retrieved quality register data and retrospective auditing of these data. No sample size calculation was performed since all patients available in the register and hospital records were used. However, a post-hoc 80% power analysis was made of study I (presented in study II) and revealed that a difference in recurrence of up to 5.7% for either group (ORH or RRH) theoretically may have remained unnoticed. In the LACC study this number was 9.5%. The time trend of improved preoperative imaging resulting in more women being treated with primary RC-T coincided with the increased implementation of RRH and in centres where both techniques (ORH and RRH) were available women with smaller tumors might have been treated with RRH and vice versa. Finally, the use of SLN biopsy and frozen section used exclusively in the RRH group led to detection and exclusion of women with occult lymph node metastases in the RRH cohort. These selection biases resulted in more advanced stages being included in the ORH cohort in study I. To try and compensate for this, separate survival analysis on subgroups, regression analysis and propensity score analysis were performed with similar results. In study II the implementation of RRH was ongoing over the entire inclusion period and should not be affected by a time trend in radiology. It is difficult to evaluate if the SLN concept introduced a selection bias in study II as it was performed in 2 of 6 centres. The impact of possible confounders such as smoking and socioeconomic status was not compensated for, the latter should have little impact due to the public health care system in Sweden. The impact of surgical skill on internal validity was part of the logistic regression model in study II. The results from study I and II should be applicable in settings where treatment for cervical cancer is centralized and performed by surgeons subspecialised in gynecologic tumor surgery with a high caseload of RRH.

The ongoing RACC-trial that randomize between ORH and RRH with extra focus on internal validity will offer further insight regarding the oncological safety of

RRH in a more general setting of cervical cancer treatment, hence also with high external validity (Falconer et al. 2019).

## Study III-V

Cervical cancer affects women of childbearing age underlining the need for fertility sparing treatment (Hamilton et al. 2015). The surgical approach for a RT largely depends on surgeons' preference with the exception that abdominal RT can be performed in larger tumors (Li et al 2013). After the results from the LACC trial, questions regarding the use of MIS in cervical cancer arose. Since trachelectomy is a rare and complex procedure a RCT is difficult to conduct. The retrospective multicenter International Radical Trachelectomy Assessment (IRTA) Study examining tumors  $\leq 2$ cm published in 2021 found no difference in recurrence rate between abdominal and MIS-RT after 4.5 years (Salvo et al. 2021). In the IRTA study, the rate of node positivity and rate of recurrence in the MIS cohort appears similar to the results presented in study III. The recurrence rates presented in recent reviews on RT appear lower than the results from study III and the IRTA study (Smith et al. 2020, Nezhat et al 2020). A direct comparison is difficult as reviews merge recurrence rates of similar surgical approaches where the individual studies included contain a vast diversity in follow-up time, patient selection and tumor risk profile (i.e. tumor size and node positivity) and whether the recurrence rate is based on an intention to treat analysis or merely on completed RT. Comparing individual studies might present a more reliable comparison. Two studies on VRT including 132 and 118 women respectively report a rate of node positivity, follow-up time and recurrence rates that appear similar to study III (Zusterzeel et al. 2016, Marchiole et al. 2007) (Table 5). Results from smaller studies are naturally more difficult to evaluate and in study V the recurrence rate was 2%.

The conception rate after RRT varies between 73-80% in study III-V. This is comparable to individual studies after both VRT and ART where rates are also calculated on women trying to conceive (Hauerberg et al. 2015, Plante et al. 2011, Wethington et al. 2012, Nishio et al. 2009). A shorter post trachelectomy cervical length may impair fertility and the high conception rate in our studies might be explained by; a high median postoperative non-pregnant cervical length where only 34% had  $< 10$ mm in study III compared with 66% after VRT (Alvarez et al. 2018), the improved visualization in robotic surgery that in our opinion favors lesser variation in cervical transection level and the beneficial effect on endometrial blood supply by sparing the uterine arteries (Egashira et al. 2018). The term delivery rate ( $\geq 36$  GW) in study III of 71% and the 86%  $\geq 32$  GW is comparable to individual studies after VRT and within the upper range reported in reviews (Hauerberg et al 2015, Nezhat et al. 2020, Smith et al. 2020, Kuznicki et al. 2021, Tirlapur et al.

2019). Direct comparisons are difficult as term delivery rates and prematurity rates are inconsistently defined.

In the cohort of women presented in study IV where the oral metronidazole/no sexual intercourse regime was applied there was no second trimester miscarriage and the rate of premature delivery was four times lower compared with women in whom the regime was not applied. The use of metronidazole has been shown to reduce the risk of preterm delivery in women with a previous history of preterm delivery (Mc Donald et al. 1997, Morales et al. 1994, Hauth et al. 1995). In women with a short cervix the presence of cervical pathogens (i.e. bacterial vaginosis and aerobic vaginitis) is associated with a higher risk of preterm delivery and preterm delivery after RRT is often preceded by premature preterm rupture of membranes, with an ascending infection as a probable triggering factor (Dowd et al. 2001, McDonald et al. 1997, Morales et al. 1994, Hauth et al. 1995). To protect the already impaired cervix from sexual intercourse, that might have adverse consequences in a group of susceptible women, could have had a beneficial effect (Sayle et al. 2001, Chabra et al. 1992). It is difficult to assess the exact mechanism behind the success of the regime, however it is a non-toxic and well-tolerated regime with excellent results on rate of prematurity, which is something every woman and clinician want to avoid (Diav-Citrin et al. 2001, Piper et al. 1993).

The incidence of cervical stenosis after RT is difficult to compare between studies since most studies do not differentiate between the often-harmless external stenosis and the internal stenosis with risk of hematometra, secondary endometriosis and infertility. In a review from 2015 of all surgical approaches of RT, a cervical stenosis was seen in 10.5% of women, consistent with the overall incidence of 14% in our study (Li et al. 2015). Internal stenosis was only diagnosed in 2-2.4% women in study III and V. This low incidence together with the probable preventive effect regarding premature deliveries supports the placement of an internal cerclage in RRT. Rejection of cerclage was associated with use of Gore-Tex suture. Severe intra and postoperative complications were absent in study V and scarce in study III, where those possible related to the robotic procedure itself were two vesicovaginal fistulae, one port herniation and one compartment syndrome of the leg.

The number of cancer survivors is growing steadily and clinical trials need to include long-term follow up to assess not only short term outcome, oncological outcome and survival but also late effects and health-related quality of life. Developing patient-reported outcome measures and disease specific questionnaires capturing the full range of issues relevant for that particular patient group is essential as demonstrated in study V (van Leeuwen et al. 2018). Reporting on global health status (GHS) in the middle of a pandemic however might have influenced the results. The GHS has been shown to vary in response to changes in the world (Sen et al. 2000). Study V included too few women and with varying follow-up time making a direct comparison to other studies difficult, however results seem to be in



line with the existing literature investigating QoL after VRT (Malmsten et al. 2019, Froeding et al. 2014). The reduced sexual and vaginal functioning and worry of dyspareunia seems in concordance with other studies that present negative impact on sexual function after treatment for cervical cancer (Bjelic-Radisic et al. 2012, Jensen et al. 2004, Schover et al. 1989). Loss of vaginal elasticity, diminished sensation, dyspareunia with secondary reduced lubrication might lead to negative effects on sexual function. However, sexual morbidity seems to improve during the first year after a radical hysterectomy with possible further improvement with time (Jensen et al. 2004, Schover et al. 1989, Frumovitz et al. 2015, Froeding et al. 2014). Despite reporting reduced sexual and vaginal functioning, the included women had a median functional score of 66.7 for both sexual enjoyment and sexual activity, the latter is to be expected in women after fertility sparing treatment and is also in accordance with other studies (Malmsten et al. 2019, Froeding et al. 2014).

Lymphedema following RRT was not objectively studied, only subjectively reported in study V and found to have a significant impact on morbidity and QoL. This has been demonstrated in previous studies (Malmsten et al. 2019 and Bjelic-Radisic et al. 2012). Lymphedema is a chronic condition that might worsen with time. If future studies can validate the preliminary results regarding oncologic safety of the SLN-concept in cervical cancer surgery the reduced rate of lymphatic complications will have a positive impact on patients QoL.

To ensure a successful outcome of fertility-sparing treatment for early stage cervical cancer, an experienced surgeon skilled in that particular complex surgical approach working in a high-volume center is key. Equally important is a careful selection of patients suitable for RT. A thorough preoperative assessment is needed to make sure the position of the tumor and remaining cervical length allows for a successful procedure. To optimize the patients' outcome and postoperative well-being, accurate information regarding reproductive outcome, sexual function, lymphedema and other possible long-term side-effect is essential. The increased risk of a second trimester miscarriage and premature delivery in future pregnancies is also important to address.

In summary study III-V suggest that RRT is oncologically safe and associated with an excellent reproductive outcome. A short postoperative cervical length was associated with a lower conception rate. When a metronidazole/no sexual intercourse regime is used the rate of second trimester miscarriage and premature delivery can be greatly reduced. Although serious adverse events are rare, side-effects such as impaired sexual function and lymphedema can have a major impact on women's quality of life. Offering adequate information to every woman suitable for a fertility sparing procedure including the possibility of a slighter higher recurrence rate than after radical hysterectomy but also the good fertility results is important.



### **Methodological considerations study III-V**

Since RRT is a relatively rare procedure a multicenter study was needed to achieve a larger material to reduce random errors. The inclusion of patients were based on local hospital registers which might introduce an information bias inevitable in retrospective studies with no existing validated international register. Selection bias might also be present in such a challenging rare procedure. As the surgeon gains more skill, larger tumors might be possible to operate for that individual surgeon. A SLN concept was used at 2 of 5 centers. However, no comparison between cohorts were made and only RRT according to NCCN and ESGO guidelines were included. Study III and V are descriptive studies with scarce statistical comparison and more hypothesis generating than hypothesis testing. There were slightly different populations included in study III and IV and hence the regression analysis on premature delivery performed in study III became somewhat irrelevant after the results of study IV. The metronidazole regime was only used at one institution (in 22/24 of pregnancies beyond the 2<sup>nd</sup> trimester) and to compensate for selection bias a regression analysis on factors possible associated with prematurity was performed. Weaknesses of the multicenter study III-IV is the lack of data (on LVSI, cervical stenosis and postoperative pre-pregnant cervical length) and the inability to guarantee internal validity of the RRT procedure. However, the included surgeons are well-known skilled robotic surgeons and the uterine artery sparing RRT procedure with an internal cerclage is clearly documented (Persson et al. 2008, Persson et al 2012). The QoL assessment in study V was only cross-sectional with a large variation in time from surgery to questionnaires (range 6-158 months) making analyses on change over time impossible. Further studies with baseline QoL, and 6 months, 1- and 2- year follow-up questionnaires after RRT is needed. Another weakness was the assessment of lymphedema which was only subjectively reported by the women responding to the questionnaire and not objectively measured.



# Conclusions

- In settings where radical hysterectomy for early-stage cervical cancer is highly centralized, no difference was found in long-term survival between open and robotic surgery.
- Increased surgical experience in robot-assisted radical hysterectomy for early stage cervical cancer resulted in a decrease in the rate of recurrence in the larger subgroup of women who did not receive adjuvant radio chemotherapy as well as in women with tumors <2 cm, regardless of whether adjuvant treatment was given or not.
- The rate of severe intraoperative and postoperatively diagnosed complications (Clavien Dindo  $\geq$  grade IIIa) decreased with increased experience in robot-assisted radical hysterectomy for early stage cervical cancer.
- In long-term follow-up of robot-assisted radical trachelectomy the recurrence rate was comparable to studies on vaginal radical trachelectomy and minimal invasive radical trachelectomy with similar tumor risk profile and follow-up time. A high pregnancy rate and low rate of premature delivery before GW 32 was seen. The baby take home rate was 72% in women trying to conceive.
- A four-fold reduction of premature delivery in pregnancies after robot-assisted radical trachelectomy was observed with an oral metronidazole regime from gestational week 15+0 to 21+6 combined with no sexual intercourse during pregnancy.
- Long term side effects, especially impaired sexual function and lymphedema can affect quality of life after robot-assisted radical trachelectomy.

# Future aspects

- To study post trachelectomy cervical length changes during pregnancy by serial measurements and if cervical length development is related to premature delivery.
- To verify the results of the metronidazole/no sexual intercourse regime on premature delivery in a prospective multicenter study.
- To further investigate quality of life and impact on sexual function after RRT by prospective serial questionnaires.
- To investigate any association between development of cervical stenosis and internal cerclage by comparison with women with internal cerclage without a concomitant trachelectomy.

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