# Robotic surgery for endometrial cancer

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**Cover illustration: Happy survivors**

**Robotic Surgery for Endometrial Cancer**

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our work should equip
the next generation of women
to outdo us in every field
this is the legacy we’ll leave behind

*progress* - rupi kaur

# Abstract

**Introduction**

Endometrial cancer (EC) is the most common gynecological malignancy, with increasing incidence worldwide. The main risk factors for developing EC include increasing age and obesity. Therefore, a large proportion of patients will be frail and at increased risk during and after surgery. Traditionally, hysterectomy by open surgery has been the treatment of choice, but in the last decades, robotic surgery has become the preferred method in many settings.

**Aim**

To investigate robotic surgery in women with EC with regard to surgical outcomes, costs, survival, and health-related quality of life (HRQoL), with special focus on obese and elderly patients.

**Methods**

*Paper I* compared robotic and open surgery (n=40/48) for EC, including surgical staging with pelvic lymphadenectomy. Patients were allocated to a surgical modality based on the hospital where they were treated. Outcomes included surgical outcome, health care costs, and return to activities of daily living (ADLs). *Papers II* and *III* compared open and robotic surgery in elderly (n=137/139) and obese (n=86/141) women treated for EC before and after the introduction of the robotic surgical system at tertiary university hospital. Surgical outcomes, postoperative complications, and long-term survival were compared. In the elderly cohort, evaluation of costs was included, while in the obese cohort details on recurrences and adjusted analyses of overall survival (OS), and disease-free survival were performed. In *Paper IV*, HRQoL was followed longitudinally for three months in a cohort of patients (n=64) undergoing primary robotic surgery for EC, using the questionnaires EORTC QLQ-C30, EN24, GAD-7, and PHQ-9.

**Results**

Robotic surgery resulted in significantly less per-operative blood loss, even in the elderly and obese patients, compared to open surgery. Length of hospital stay was reduced after robotic surgery, with a median length of 2 vs 5 days ($p<0.001$) for the elderly and 1 vs 5 days ($p<0.001$) for the obese patients. The relative risk of postoperative complications (CD grade II-V) was 0.54 (95% confidence interval (CI) 0.31-0.93) after robotic compared to open surgery in the obese patients. In the elderly patients, robotic surgery reduced the CD grade II complication rate from 22% to 10% ($p=0.006$) compared to open surgery. There was no significant difference in mean costs between the surgical modalities. Overall survival in the elderly patients was 69% (95% CI 62–78) for the open surgery group and 77% (95% CI 68–86) for the robotic surgery group. For the obese patients, OS was 76% (95% CI 67–85) vs 87% (95% CI 82–93) for the open and robotic surgery group, respectively. In a multivariable analysis of OS in the obese cohort, surgical modality was not found to be an independent risk factor. When analyzing HRQoL, patients' global health status was significantly lower 2 weeks after surgery and returned to baseline levels at 3 months. The proportion of patients scoring above the clinical threshold (≥10) for anxiety and depression was 27% and 20% at baseline; but returned to levels equivalent those found in women in the general population after 2 weeks.

**Conclusion**

Robotic surgery for EC reduced the risk of postoperative complications compared to open surgery in obese and elderly. There was no difference in long-term survival or health care costs between the surgical modalities. HRQoL was reduced in the immediate postoperative period after robotic surgery for EC, but baseline levels were regained within 3 months. These results indicate that robotic surgery should be the recommended surgical modality in treating women with EC, including obese and elderly women.

# Sammanfattning på svenska

Endometriecancer (EC), eller ofta kallad, livmoderkroppscancer, är den vanligaste gynekologiska cancersjukdomen. Hög ålder och fetma är två betydelsefulla riskfaktorer för att utveckla sjukdomen, och en stor andel av drabbade patienter uppvisar dessa karaktäristika. Behandling för EC består i huvudsak av kirurgi, vilket innebär borttagande av livmoder och äggstockar. Detta har traditionellt sätt utförts via öppen kirurgi men sedan robotkirurgin introducerades har denna titthålsteknik utvecklats och är numera den främst använda metoden på många håll.

Syftet med denna avhandling var att studera effekten av robotkirurgi hos kvinnor med EC, avseende kirurgiska utfall, sjukvårdskostnader, överlevnad och hälso-relaterad livskvalitet, med särskilt fokus på patienter med hög ålder och fetma.

I Paper I-III jämfördes resultat efter kirurgi hos patienter som genomgått robotkirurgi eller öppen kirurgi. Paper II studerade specifikt äldre patienter (≥70 år) och Paper III patienter med fetma (BMI ≥30m$^2$/kg). Paper IV studerade hälsorelaterad livskvalitet och symtom på depression och ångest över tid, hos kvinnor som nyligen diagnosticerats med EC som alla genomgått robotkirurgi.

Studierna visade att robotkirurgi resulterade i mindre blödningsmängd under operationen och kortare vårdtid på sjukhus, också hos äldre och patienter med fetma. Hos patienter med fetma, minskade risken att drabbas av en komplikation med 46 % efter robotkirurgi jämfört med öppen kirurgi. Hos äldre sågs en minskning av andelen som fick en mild komplikation (10% jämfört med 22%). Det fanns ingen skillnad i sjukvårdskostnaderna för de två kirurgiska metoderna i dessa studier. Den totala 5-årsöverlevnaden hos de äldre var 69% efter öppen kirurgi och 77% efter robotkirurgi. Hos kvinnor med fetma var 5-årsöverlevnaden 76% jämfört med 87% för öppen respektive robotkirurgi. Vid fördjupade analyser hos kvinnor med fetma, framkom det dock inte att kirurgisk metod var avgörande för risken att dö eller drabbas av återfall i EC. Livskvalitet, mätt som Globalt hälsostatus var sänkt 2 veckor efter operation, men återgick till normalnivå inom 3 månader. Andelen patienter som angav depressions- och ångestsymtom över en kliniskt relevant nivå var 20% respektive 27% vid utgångsmätningen, just innan operationen, men återgick till nivåer motsvarande de i den generella befolkningen efter två veckor.

Sammantaget uppvisade studierna fördelaktiga kirurgiska utfall efter robotkirurgi, jämfört med öppen kirurgi, även hos de med hög ålder eller fetma. Samtidigt fanns likvärdiga sjukvårdskostnader och överlevnadsresultat för de två metoderna. Patienters livskvalitet påverkades övergående i anslutning till, och just efter operationen, men utan kvarstående negativa effekter. Utifrån resultaten i denna avhandling bör robotkirurgi utgöra den rekommenderade förstahandsmetoden vid kirurgi för EC, även hos kvinnor med hög ålder eller fetma.

# List of publications

**This thesis is based on the following studies, referred to in the text by their Roman numerals:**

**I. Eklind S, Lindfors A, Sjöli P, Dahm-Kähler P.**
A prospective, comparative study on robotic versus open-surgery hysterectomy and pelvic lymphadenectomy for endometrial carcinoma. Int J Gynecol Cancer 2015, Feb;25(2):250-6

**II. Lindfors A, Åkesson Å, Staf C, Sjöli P, Sundfeldt K, Dahm-Kähler P.**
Robotic vs Open Surgery for Endometrial Cancer in Elderly Patients: Surgical Outcome, Survival, and Cost Analysis**.** Int J Gynecol Cancer. 2018 May;28(4):692-699

**III. Lindfors A, Heshar H, Adok C, Sundfeldt K, Dahm-Kähler P.**
Long-term survival in obese patients after robotic or open surgery for endometrial cancer. Gynecol Oncol. 2020 Sep;158(3):673-680

**IV. Lindfors A, Järvholm S, Dahm-Kähler P.**
Health-Related Quality of Life after Robotic Surgery for Endometrial Cancer – a Prospective Longitudinal Follow-up. *Submitted*

# Contents

# Abbreviations

| | |
|---|---|
| ADLs | activities of daily living |
| ASA | American Society of Anesthesiologists |
| BMI | body mass index |
| BSOE | bilateral salpingo-oophorectomy |
| CCI | Charlson Comorbidity Index |
| CD | Clavien-Dindo |
| CI | confidence interval |
| CPP | cost per patient |
| DFS | disease-free survival |
| EBL | estimated blood loss |
| EC | endometrial cancer |
| EN24 | Quality of Life Questionnaire Endometrial cancer 24 |
| EORTC | European Organization for Research and Treatment of Cancer |
| ERT | external radiotherapy |
| FIGO | International Federation of Gynecology and Obstetrics |
| GAD-7 | General Anxiety Disorder Assessment |
| GHS | global health status |
| HR | hazard ratio |
| HRQoL | health-related quality of life |
| LAP2 trial | Laparoscopy compared with Laparotomy for Comprehensive Surgical Staging of Uterine Cancer trial |
| MIS | minimally invasive surgery |
| NGEC | national guidelines for endometrial cancer |
| OS | overall survival |
| PPLND | pelvic and para-aortic lymph node dissection |
| PHQ-9 | Patient Health Questionnaire 9 |
| PRO | patient-reported outcome |
| QLQ-C30 | Quality of Life Questionnaire Core 30 |
| QoL | quality of life |
| RCT | randomized controlled trial |
| RFS | recurrence-free survival |
| RS | relative survival |
| SD | standard deviation |
| SLN | sentinel lymph node |
| SQRGC | Swedish Quality Register for Gynecological Cancer |
| SUH | Sahlgrenska University Hospital |
| WHO | World Health Organization |
| WSHCR | Western Sweden Health Care Region |

# 1. Introduction

## 1.1 Epidemiology

Endometrial cancer (EC) is the most common gynecological malignancy in the industrialized world, with an estimated 320 000 women worldwide diagnosed annually.[1] In Sweden, EC is the sixth most common cancer in women, with about 1400 new cases yearly.[2] Mainly postmenopausal women are diagnosed, the median age at diagnosis being 70 in Sweden.[2, 3]

The age-standardized incidence rates vary between one and 30 per 100 000 women globally; the highest rates are found in Europe and North America and the lowest in the developing countries (Fig. 1). Low rates of EC are also observed in Sub-Saharan countries, the Middle East, and south-central Asia.[1] In the majority of countries, the age-standardized rates of EC have increased over the last years. The most rapid increase from 2001 to 2010 was seen in countries with the lowest rates at the start, where a doubled incidence rate has for example been seen in South Africa in 10 years. During the same period, some countries, mainly in Northern Europe, have shown no change in incidence rates, while some, Sweden and Austria included, have exhibited a decreasing incidence trend.[1]

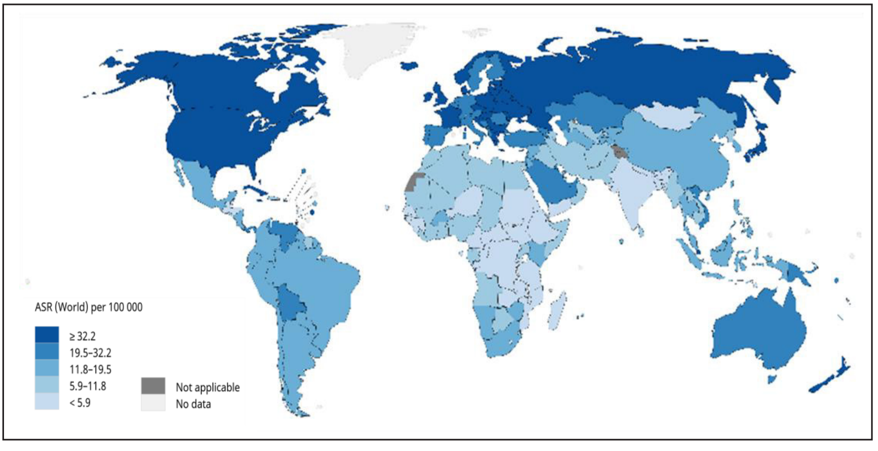


**Figure 1.** Worldwide age-standardized incidence of endometrial cancer per 100 000 women, in 2020, ages ≥30 years. Source: GLOBOCAN [4]

Lifestyle factors are thought to be causing the increase seen in the Western world, since risk factors for EC include obesity, diabetes mellitus, late menopause, and an aging population. However, discrepancies between an increase in obesity rates and EC incidence in some countries indicate a combined influence of several risk factors on EC development.

## 1.2 Etiology

As the name suggests, EC originates from the endometrium, the lining of the corpus uteri. Traditionally, the development of EC has been divided into two different pathways, type I and type II, with clinical and genetic differences. The majority of patients (>80%) have type I EC, which is associated with hyperestrogenism and associated with good prognosis. Type I EC tumors are moderately or well differentiated endometrioid and often superficially invasive. Endometrial hyperplasia with atypia is a precancerous condition, preceding or coexisting with type I tumors, and has a high potential to develop into cancer. The remaining patients, about 20%, have type II, non-hormone-dependent, low differentiated endometrioid adenocarcinomas and other less common histology types. They have a less favorable prognosis.

One main risk factor for EC is exposure to endogenous and exogenous estrogens, which may explain some of the increased incidence.[5] In premenopausal women, estrogens are mainly produced by the ovaries. In postmenopausal women, androgens are converted to estrone and estradiol in peripheral tissue, including fatty tissue, by aromatase.[6] Aromatase is produced by mesenchymal stromal cells, including adipocyte stem cells, and its level increases as a function of age and obesity. Estrogens have a proliferative effect on the endometrium in the absence of progesterone, and therefore promote hyperplasia and progression to cancer. In addition, the level of sexual hormone-binding globulin (SHBG) declines with obesity and this glycoprotein binds both estrogens and progesterone and hence influences the biological activity of these two hormones irrespective of synthesis. Endogenous exposure to estrogens is seen in early menarche, late menopause, nulliparity, obesity, and older age. These factors seem to be increasing in most parts of the world, with a link to obesity and lifestyle factors, including increased sedentary time.[6] Moreover, obesity is an independent risk factor and associated with 35% or more of cases of EC in the Western world.[7]

Exogenous exposure to estrogens in peri- and postmenopausal women has been fluctuating during the last decades, and could hence affect trends seen in incidence.[8] Patients substituted with unopposed estrogen in menopause have been shown to have a sixfold higher risk of EC after a 5-year treatment whose effects last up to 10 years after therapy is abandoned.[9] These results, together with findings of increased risk of breast cancer, have led to a drop in the use of menopausal hormones shortly after the millennium shift. Other risk factors for EC include hypertension, diabetes mellitus, infertility, and tamoxifen.[5]

On the other hand, protective factors could mitigate some of the increased incidence. Oral contraceptives, being a protective factor for EC, may contribute to the decline in EC incidence seen in some countries over the last years. With every 5 years of use, a risk decline of 24% is seen, which lasts for more than 30 years after cessation.[10, 11] Smoking decreases the risk of EC in postmenopausal women, but this does not outweigh the harmful effects of this habit.[12] Type II tumors, being non-hormone-dependent, still share some risk factors with type I EC, namely, nulliparity, early menarche, and diabetes, as well as sharing the protective effect of smoking and oral contraceptives.[13]

Women with Lynch syndrome, diagnosed on the basis of a mutation in a mismatch repair gene (MLH2, MSH2, MSH6, or PMS2) have a lifetime risk of EC of 40-60%.[14] Endometrial cancer due to Lynch syndrome accounts for 1–5% of all cases of EC and the median age of onset in this group is 48 years. These women are therefore recommended regular screening and prophylactic hysterectomy and salpingo-oophorectomy when reaching menopause or at 40 years of age or after finishing childbearing in premenopausal carriers.[15, 16]

## 1.3 Tumor diagnosis and classification

The first symptoms of EC are abnormal bleeding or discharge, which often is a symptom that leads to early diagnosis. The disease is mainly diagnosed via transvaginal ultrasound in combination with an endometrial biopsy. Sampling of the endometrium via blind endometrial biopsy is the diagnostic method of choice, due to high accuracy compared to dilatation and curettage (D&C), and easily accessible in a polyclinic setting. When an endometrial biopsy is not possible to obtain, a D&C can be performed.[17, 18] Hysteroscopy is an alternative method and should be used in case of suspected focal findings or when standard methods are inconclusive. This method has been shown to have an overall success rate of 96%.[19] The cancer diagnosis should lead to prompt planning of surgery and preoperative work-up including imaging and evaluation of operability based on the individual patient characteristics.

Endometrial cancer is histologically classified according to the World Health Organization (WHO) classification, and divided into the most common endometrioid adenocarcinoma and the more uncommon, but high-risk, non-endometrioid histological subgroups: serous, clear cell, carcinosarcoma, and dedifferentiated and undifferentiated carcinomas.[20] Endometrioid adenocarcinomas (which includes mucinous adenocarcinomas) constitute about 80% of all ECs. They are graded, according to the WHO classification of tumors, into International Federation of Gynecology and Obstetrics (FIGO) Grade 1 (50%), Grade 2 (35%), and Grade 3 (15%), where a low-grade tumor has a more favorable prognosis and higher differentiation.[2] A diagnosis of hyperplasia with atypia is known to present with a coexisting low-grade tumor in 30% of cases.

Staging in EC is done surgically and according to the 2009 revised FIGO staging system.[21] In the Swedish cohort from 2010–2014, 76% were classified as stage I, 8% as stage II, 10% as stage III, and 5% as stage IV. In less than 1% was the stage unknown.[2]

**Table 1.** Surgical stage according to the International Federation of Gynecology and Obstetrics (FIGO) 2009 staging system

| Stage | Tumor |
|---|---|
| **I** | **Tumor defined to the corpus uteri** |
| IA | Tumor invasion <50% of the myometrium |
| IB | Tumor invasion ≥50% of the myometrium |
| **II** | **Tumor invasion of the cervical stroma; no tumor outside of the uterus** |
| **III** | **Local and/or regional spread of the tumor** |
| IIIA | Tumor invasion of the serosa and/or vagina |
| IIIB | Tumor growth to the vagina and/or parametrial involvement |
| IIIC1 | Metastasis to pelvic lymph nodes |
| IIIC2 | Metastasis to para-aortic lymph nodes |
| **IV** | **Tumor invasion of the bladder and/or bowel mucosa, and/or distant metastasis** |
| IVA | Tumor invasion of the bladder and/or bowel mucosa |
| IVB | Distant metastasis |

The FIGO staging system is based on how far the tumor advances locally and regionally, and on distant metastasis and lymph node involvement, Table 1. Stage I is confined to the uterus. Stage II advances to the cervix. Stage III spreads outside of the uterus; to the uterine serosa, to the adnexa and/or vagina, or to lymph nodes. Stage IV is the most advanced stage, with invasion of the bladder or bowel mucosa, or distant metastasis.

Attempts have been made to preoperatively differentiate which patients are at higher risk of lymph node metastasis, and thus identify which patients should be offered a more extensive staging procedure with lymphadenectomy to tailor adjuvant treatment. Lymph nodes are assessed either only in the pelvic region or in the pelvic station in combination with para-aortic stations. The more extensive the lymphadenectomy procedure, the more surgical access is needed. This subsequently demands higher surgical skills and carries risk of surgical morbidity in the patient.

Recent technical developments and research have led to the sentinel lymph node (SLN) technique, which long has been a standard practice in other diagnoses (breast cancer and vulvar cancer). The SLN technique has the advantage of less dissection and, hence, less surgical trauma. This gives the possibility to offer a lymph node assessment and, therefore, more accurate staging, to all EC patients, instead of the often insufficient, preoperative classification into high- and low-risk tumors.[22-25] Detection rates of between 52% and 95% have been reported, depending on surgical experience.[26] Ideally with the SLN technique, the 5% of patients with low-risk disease who still have node metastases can be identified, receive adjuvant therapy, and have a chance of better prognosis.[24] Simultaneously, patients with high-risk disease may be staged more accurately thanks to ultra-staging of nodes and immunohistochemistry, performed by pathologists, an advantage in addition to the decreased surgical burden.[27]

## 1.4 Prognostic factors

The majority of patients with EC are diagnosed at an early stage, which is reflected in the generally favorable prognosis (Fig 2). The relative survival (RS) for EC in Sweden 2013-2019, was 81% (95% Confidence interval (CI) 80-82), all stages included. The corresponding rate for overall survival (OS) was 72% (95% CI 71-73).

The risk of recurrence is highest during the first 3 years; after 5 years, only a small portion of patients present with recurrence. In the light of this, numbers on 5-year survival are relevant.

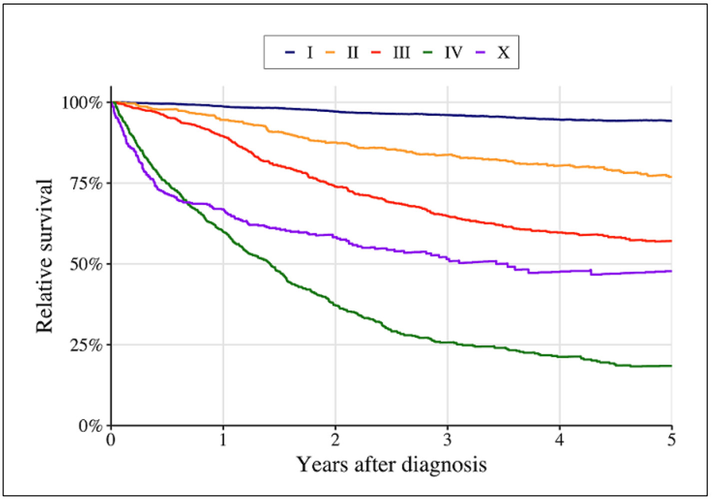


**Figure 2.** Relative survival per stage in Sweden, 2013–2019
X=stage not reported
Source: Swedish Quality Register for Gynecological Cancer (SQRGC)[28]

**Table 2.** Relative 5-year survival per stage in Sweden, 2013-2019

| FIGO stage | 5-year RS % | 95% CI |
|---|---|---|
| I | 94.2 | 93.1 - 95.3 |
| II | 76.9 | 72.4 - 81.7 |
| III | 57.1 | 53.5 - 61.0 |
| IV | 18.5 | 15.1 - 22.7 |
| X | 47.9 | 40.6 - 56.4 |

CI=confidence interval; FIGO=International Federation of Gynecology and Obstetrics; RS=relative survival
X=stage not reported. Source: Swedish Quality Register for Gynecological Cancer (SQRGC)[28]

The majority of patients will be considered cured after primary surgery, and, according to postoperative risk assessment, not recommended further adjuvant treatment. With today's risk stratification, 9% of low-risk patients will have recurrence, while 60% of patients at high risk will not.[29] Therefore, it is desirable to identify an improved version of the current stratification system. The SLN technique described above may contribute to this.

Stage is known to be the strongest independent prognostic factor. Other factors decisive for prognosis are histological subtype, differentiating grade, age, and lymphovascular space invasion (LVSI). In the current national guidelines, stage, non-endometrioid histology, FIGO stage ≥III, and deep myometrial invasion are taken into consideration when deciding on adjuvant treatment, due to increased risk of recurrence.[2]

Other prognostic factors include deoxyribonucleic acid (DNA) ploidy, tumor size, and different molecular characterizations of the tumor. Extensive research has been done on genomic subgroups of EC and different groups have published work suggesting three immunohistochemical markers (p53, MSH6, and PMS2) and one molecular test (mutation analysis of the exonuclease domain of polymerase epsilon (POLE)), to be used as prognostic features in addition to the current prognostic factors.[30] In the 2020 updated consensus guidelines on EC from the European Society of Gynaecological Oncology (ESGO), the European Society for Radiotherapy and Oncology (ESTRO), and the European Society of Pathology (ESP), ESGO-ESTRO-ESP, molecular classification is recommended in all EC patients in settings where it is available.[31]

## 1.5. Surgery

The basis for primary treatment of EC is surgery with hysterectomy and bilateral salpingo-oophorectomy (BSOE). In selected cases, with the purpose of staging of the disease, additional lymphadenectomy and omental resection is done.[31]

Traditionally, the procedure has been done through open surgery and laparotomy, but as surgery evolved, this has been adapted accordingly. Minimally invasive surgery (MIS), and conventional laparoscopy, has its roots in gynecology. When a video screen was introduced in the 1980s, the technique gained acceptance and became established. The first laparoscopic hysterectomy was performed in the late 1980s and the technique has since rapidly developed, including MIS in gynecologic oncology.

In 2009, a large randomized trial, the Laparoscopy compared with Laparotomy for Comprehensive Surgical Staging of Uterine Cancer (LAP2) trial, was published where 2616 patients were randomized (2:1) to either conventional laparoscopy or open surgery.[32] Patients underwent comprehensive staging including pelvic and para-aortic lymph node dissection (PPLND), however with a conversion rate of 25.8%. The risk of conversion increased both with increasing body mass index (BMI) and increasing age. A significantly longer operative time was reported for laparoscopy compared to open surgery. No differences were reported regarding intraoperative complications, but significantly fewer moderate and severe postoperative complications (14% vs 21%), as well as shorter hospitalization, were shown for laparoscopy. This study became a corner stone for the change in standard of care for EC towards minimally invasive techniques.[33] Later, data on recurrence and survival from the LAP2 trial was published, reporting results that MIS is safe in a longer oncological perspective.[34] A second large randomized trial was published by Janda and colleagues in 2017, the Laparoscopic Approach to Cancer of the Endometrium (LACE) trial.[35] A total of 760 patients with stage I EC were randomly assigned to total hysterectomy by open surgery or total laparoscopic hysterectomy. The authors concluded that disease-free survival (DFS) and OS were equivalent.

Minimally invasive procedures are now recommended for early-stage EC.[31] In Sweden, conventional laparoscopic surgery for treatment and staging of EC was never an established technique before the introduction of robotic surgery. Possibly because of generally low-volume settings, as a result of the country's demographics, the modality has been considered complex and has been believed to require a long learning curve for the more challenging procedures. Therefore, until robotic surgery was introduced, open surgery was the modality of choice.

### 1.5.1 Robotic surgery

The concept of a robotic arm to replace human movements first entered medical surgery in 1978 when the Programmable Universal Manipulation Arm (PUMA) was used to orient a needle for a brain biopsy during a neurological surgery.[36] In 1998, the Zeus® became commercially available for telerobotic-assisted surgery. It was the result from a development of the Automated Endoscopic System for Optimal Positioning (AESOP) robotic platform. This system essentially enabled surgeons to voice control the positioning of a laparoscopic camera system. The surgeon sat on a console at a distance from the robot which had three robotic arms attached to the table, including the optic system, and remotely operated on the patients. Computer Motion, the developers of Zeus®, later merged with Intuitive Surgical in 2003. At the time, Zeus® was most prominently used in cardiac surgery. The Da Vinci system was developed in parallel. It began as a US government-run project for improving surgical capabilities in the battlefield using telepresence surgery, and hence keeping the surgeon at a safe distance when performing the procedure.[37] The Da Vinci® system (Intuitive Surgical, Inc., Sunnyville, CA, USA) was approved by the US Food and Drug Administration (FDA) for general laparoscopic procedures in 2000, and for gynecological indications in 2005. Since then, the robotic-assisted laparoscopic technique, hereafter referred to as "robotic surgery," has taken landmark steps and steadily increased in use.

The robotic system enables a laparoscopic technique with beneficial ergonomic features and dexterity for the surgeon and supposedly shorter surgeon learning curve.[38] The surgical instruments, led by the surgeon in the console, but facilitated by the robotic arms, improves surgical precision through wide range of movements with wristed instruments, cancelled natural tremor and three-dimensional stereoscoptic vision. To gain optimal surgical access, the technique requires the patient to be in steep Trendelenburg position (defined as 25–30 degrees), but also allows a lower pressure of the pneumoperitoneum due to an elevation of the abdominal wall by the robotic arms. Figure 3 visualizes the robotic system docked to the patient. The rapid change in surgical modality to robotic technique, without evidence of superiority, probably also reflects a willingness of surgeons to adapt to new technologies. The first period of a robotic surgical system in a setting will encompass procedures performed before surgeons have gained sufficient experience from the novel technique. The impact of surgical training has mainly been followed through operative times, but affects other outcomes as well. In early cervical cancer treated by radical hysterectomy, increased survival has been observed, after a plateau in the learning curve of robotic surgery for the surgical team.[39] The learning curve for EC depends obviously on how extensive the procedure is, i.e., if staging including pelvic lymphadenectomy, full PPLND or SLN is performed. The surgical experience before going into robotic surgery will also be crucial. A range of 24 to 50 cases has been suggested as a requirement for an experienced laparoscopic surgeon to become proficient in staging of EC using robotic surgery.[26, 38]

An early study by Boggess et al. presented a comparison of 138 patients undergoing open and 103 undergoing robotic surgery for EC.[40] They found a significantly shorter operative time, less blood loss, and shorter length of stay in favor of robotic surgery. In addition, an increased lymph node yield and fewer postoperative complications after robotic surgery were seen. Since then, many observational studies comparing robotic surgery to other modalities have been conducted. There is observational data to conclude that robotic surgery in the general EC population seems to have benefits regarding amount of bleeding and, hence, need for blood transfusion, hospital length of stay, and possibly postoperative complications, compared to open surgery. Whether operative time and, hence, occupation of the operating theater constitutes a difference, is not unambiguous.[40-44]

Few randomized controlled trials (RCTs) are available on robotic surgery compared to open surgery for EC. Salehi et al. conducted an RCT in 48 robotic and 48 open surgery patients undergoing staging for EC including infrarenal lymphadenectomy.[45] They concluded that robotic surgery resulted in longer operative time, less blood loss, and shorter hospital stay. The number of harvested lymph nodes was the same, as was presence of intra- and postoperative complications, while the robotic approach resulted in lower health care costs. It should be noted that their study was based on procedures with extensive surgical dissections, to retrieve infrarenal nodes, which is not the case for most EC patients in Sweden and is likely to become even less common with the introduction of SLN as standard technique.

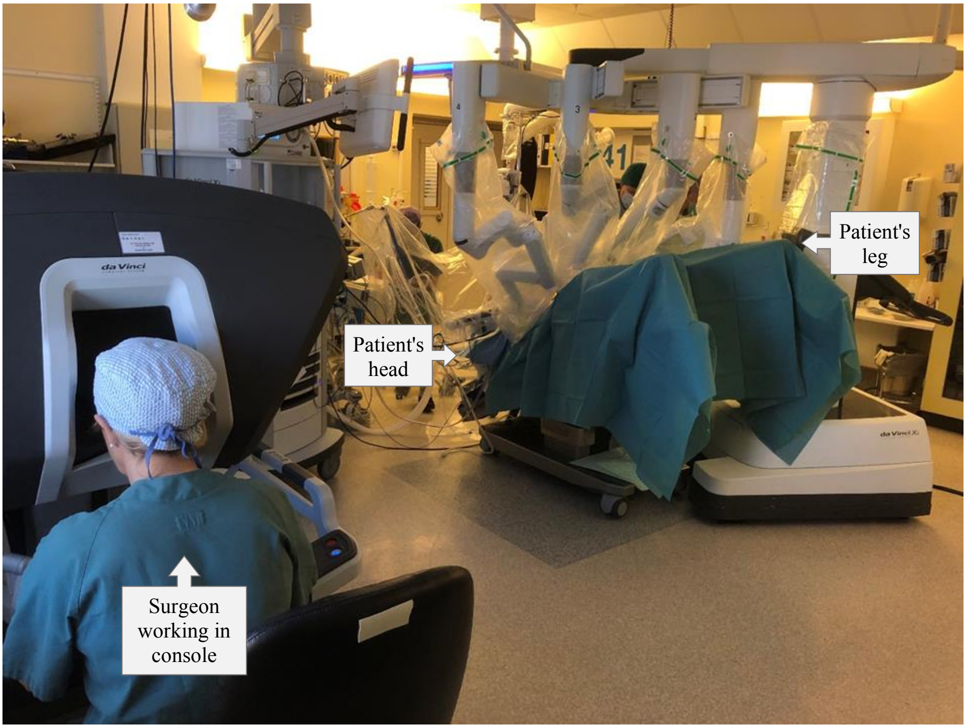


**Figure 3.** Patient under general anesthesia on the surgical table in steep Trendelenburg position. Robotic surgical system docked to the patient and surgeon working in the console at a distance from the patient
*Photo by Charlotte Palmqvist*

### 1.5.2 Health care costs

Swedish health care is public and organized to promote cost effectiveness. The Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) evaluates health technologies, which work also involves an economic perspective.[46] This includes not only the actual costs, but also medical benefits and, ideally, economic incentives for society. This evaluation is a complex issue of political economic science and is not fully explored in this thesis.

The health care costs of robotic surgery have accordingly been a theme for debate due to high costs for acquisition and maintenance and single-use instruments, which drive costs. On the other hand, these increased costs are counteracted by the decreased costs due to shorter hospital stay. Measuring and comparing costs between institutions is complicated because of differences in methodology and also in organization of health care and financing. Early reports of robotic surgery indicated that the new surgical method was accompanied by higher costs compared to alternative methods.[47-49] Over time, as surgeons' experience has increased and robotic systems have been utilized more efficiently, the additional costs have decreased. Later reports have shown more equal costs for robotic surgery and open surgery, but still there is no consensus on how robotic surgery affects the total burden of health care costs.[50]

In 2009, before the introduction of robotic surgery in gynecologic oncology, the Health Technology Assessment (HTA) Center of Western Sweden evaluated costs for cervical cancer and EC procedures. It concluded that, at the time, the scientific documentation of a potential beneficial effect of robotic surgery, compared to open and conventional laparoscopic surgery, was insufficient. However, it added that robot surgery was possibly a cost-efficient modality, due to reduced costs for hospital stay. The increased cost per treatment was estimated to be 26 500 SEK (3042 USD at a rate of 1 USD=8.71 SEK) for the new technique and simultaneously the procedure was assessed to possibly save 21 900 SEK (2514 USD).[51]

## 1.6 Survival and recurrence

The prognosis and, hence, survival are considered generally good after treatment for EC. Ultimately, the treatment aims to optimize survival including DFS. Long-term outcomes for conventional laparoscopy have been evaluated in the randomized LAP2 trial, with similar results on recurrence and OS, compared to open surgery, in the general EC population (OS 89.8% in both arms).[34] For robotic surgery for EC, there are no randomized trials available assessing long-term oncological results. Register-based studies and retrospective chart reviews have reported equivalent, or even better, long-term survival outcomes for robotic surgery compared to open surgery and conventional laparoscopic surgery, but data are limited.[52-54]

Up until now, gynecologic surgeons have relied on the theory that robotic surgery offers a clinical situation similar to conventional laparoscopic and open surgery and, hence, corresponding long-term survival results. Lately, however, there have been reasons to question long-term results in gynecological cancer surgery, due to the results from a randomized trial evaluating MIS and open surgery after radical hysterectomy for cervical cancer, referred to as the "Laparoscopic Approach to Cervical Cancer (LACC) trial".[55] Interestingly, and quite surprisingly, the study showed that long-term outcomes including both DFS and OS were compromised after MIS, compared to open surgery. Notably, 84.4% surgeries were performed by conventional laparoscopy and only 15.6% by robotics. There is no study, so far, indicating a similar situation for total hysterectomy for EC and neither is there any evidence yet to prove that robotic surgery is non-inferior to open surgery in terms of long-term survival outcomes. Therefore, studies on EC reporting long-term oncological results of the different surgical techniques are valuable and of great importance.

## 1.7 Quality of life

Health-related quality of life (HRQoL) is an important consideration in cancer care, and gives insight into patients' experience of care and symptoms related to the diagnosis and treatment. A special interest in and awareness of health issues, reported directly by the patient, termed patient-reported outcomes (PROs), have been seen. In EC, HRQoL is of great importance, considering the high survival rate and, hence, the large population of survivors with a high life expectancy after cancer treatment. EC often comes with other factors that can influence HRQoL negatively, such as obesity, high age, and other comorbidities.[56] The initial obvious physical limitations after surgery are accompanied by stress, fatigue, changes in sexual functioning, and other treatment-specific symptoms, which may affect the post-treatment period for cancer patients.

Depression and anxiety have been shown to affect patients undergoing cancer treatment in general. Symptoms are mainly related to psychological reactions to the diagnosis and treatment; and a direct neuropsychiatric impact of the cancer and its treatment has also been described.[57] Emotional stress has been reported to impact compliance with adjuvant treatment and may affect the prognosis.[58-60]

There are studies focusing on HRQoL in EC survivors, but few have used a validated questionnaire or evaluated patients' symptoms of depression and anxiety after treatment. Valid longitudinal studies are also scare, with many being cross-sectional at heterogenous time points, or with a lower retention over time.[61] Focusing on colorectal cancer, one RCT has indicated that MIS is favorable compared to open surgery with regard to HRQoL.[62]

Still little is known about HRQoL in EC patients, and about their experience of undergoing robotic surgery. Knowledge about HRQoL after treatment for EC is instrumental for the clinician to adequately inform patients and provide specific interventions and offer support.

## 1.8 Oncological treatment

Patients are offered adjuvant therapy based on risk classification after the surgical staging, with the aim to reduce recurrence and improve survival. Chemotherapy, external radiotherapy (ERT), and internal radiotherapy (brachytherapy) are possible modalities, alone or in combination. Receiving adjuvant therapy is not risk-free and these modalities are associated with both acute and delayed toxic effects. Whom to offer adjuvant therapy has no international consensus due to lack of evidence, though there are guidelines by the European Society of Gynaecological Oncology (ESGO), the European Society for Radiotherapy and Oncology (ESTRO) and the European Society of Pathology (ESP).[31]

In Sweden, the first national guidelines for endometrial cancer (NGEC) were published in 2013 and since then the guidelines have been regularly updated.[2] The NGEC is an evidence-based cancer care program, written by a national, multidisciplinary board. Before the implementation of the NGEC, regional guidelines were in use to standardize cancer care.[63] In the present version of the NGEC, the prognostic factors decisive for postoperative adjuvant therapy are: stage, non-endometrioid histology, high grade, and deep myometrial invasion. On the basis of this, the current NGEC suggests adjuvant chemotherapy and/or ERT for patients with: stage I with non-endometrioid histology, stage II with more than one risk factor, or non-endometrioid histology and stage ≥III. During the study period, when patients in Paper I–III were under treatment, risk classification for adjuvant therapy in addition included p53-status, s-phase fraction, DNA ploidy, LVSI, and age, in accordance with regional protocols.

During the study period, brachytherapy was still a commonly used modality, although since the new NGEC it has been omitted to a large extent.[64] Today, the postoperative adjuvant treatment for EC consists of the standard combination of chemotherapy with carboplatin and paclitaxel, with possible addition of ERT or brachytherapy. Both these modalities are associated with negative side effects in all patients, troublesome for many. In the light of this, it would be of utter importance to have scientific evidence to guide who should be offered these regimens.

## 1.9 Obesity

Obesity has globally doubled since the 1980s.[65] Obesity is classified according to BMI, using the WHO classification:[66]

| BMI, kg/m2 | Classification |
|---|---|
| <18.5 | Underweight |
| 18.5–24.9 | Normal weight |
| 25.0–29.9 | Overweight/preobesity |
| 30.0–34.9 | Obesity class I |
| 35.0–39.0 | Obesity class II |
| ≥40 | Obesity class III |

The largest increase in mean BMI in women over the last 40 years has occurred in Central Latin America. Other countries with prominent increases in obesity prevalence include high-income English-speaking countries and South East Asia.[67] In the US, the rate of obesity (BMI ≥30 kg/m$^2$) increased from 30% in 2000 to 42% in 2018.[68] In Europe, the proportion of obese women varies between countries, from 10% to 28%, with Sweden being among the countries with lower rates, estimated at 15% in 2014.[69] Risk of obesity increases with age. In Sweden, in the age group 45-84 years, 19% are obese.[70] Obesity is considered a risk factor in surgery and a relative contraindication to general anesthesia, and is associated with a higher prevalence of comorbidities, mainly cardiovascular diseases, diabetes, and other cancers.[71]

In colorectal cancer surgery, obese patients have been shown to be at increased risk of postoperative infections but some data on long-term oncological outcomes after colorectal cancer surgery are equivalent in obese and non-obese patients.[72-74] Moreover, in colorectal surgery, obesity is shown to be associated with attempting MIS less often and a higher conversion rate to open surgery in cases of laparoscopy. Explanatory factors, in addition to the obvious deeper wound, may include decreased wound oxygenation, inadequate tissue concentrations of antibiotics, lower immune function, and procedural difficulties resulting in contamination and prolonged operative time.[75] Publications are also suggesting that laparoscopic procedures decrease the risk for postoperative infections in obese patients, compared to open surgery, for general abdominal procedures.[76] Obese patients are believed to have worse tolerance for techniques requiring steep Trendelenburg position, including robotic surgery. These factors may partly explain why obese patients are not offered the standard of care to the same extent as normal weight patients.

In EC, obesity is present in about half of patients and these patients present a surgical challenge because of their size and associated characteristics.[77] Obesity places a patient at increased risk of developing EC, and possibly at increased risk when undergoing surgery. Gynecologic oncology surgeons have been hesitant to offer obese patients MIS techniques to the same extent as non-obese patients, and the same trend regarding fewer lymph node dissections in obese patients has been reported.[78] With increasing numbers of obese women, and an aging population, we can expect to see an increased incidence of patients with these characteristics. In obese patients with EC, a lower proportion are diagnosed with high-risk histologies, which is associated with favorable prognosis, but simultaneously obesity has been shown to be associated with lower quality of life (QoL).[61, 79]

## 1.10 Elderly

The risk of EC increases with age. In Sweden, the median age at diagnosis is 70 years, resulting in a considerable part of the EC population being older. With greater age comes increased risk of comorbidities and other factors associated with postoperative complications and mortality. Whether increased age itself constitutes a risk factor for postoperative morbidity and mortality is unknown.[80]

Findings from other fields of surgery indicate that age is an independent risk factor, though not well studied. In breast cancer, which is generally associated with low rates of complications, elderly patients have been shown to present with higher rates of postoperative complications, although not mainly wound-related. Simultaneously, studies show that elderly patients diagnosed with breast cancer are recommended standard surgical treatment less often, and choose to opt out of surgery to a larger extent when advised to do so.[81, 82] For colorectal cancer, data are contradictory. Earlier reports concluded that age was a risk factor for postoperative complications and OS after colorectal cancer surgery.[83] Age-related differences are less obvious in cancer-specific survival. It has also been shown that elderly patients undergo curative surgery less often. More recently, however, it has been suggested that standard surgical approach should be used in elderly patients and that advanced age itself is not a prognostic factor for outcomes after colorectal cancer.[84] Being elderly and having comorbidities, or encountering postoperative complications, correlates with increased risk of 1-year mortality after colorectal cancer surgery.[85] This makes early ambulation and recovery after surgery a great benefit, to be strived for in this group of patients. It has been proposed that organ systems in elderly people do not meet the increased functional demands when undergoing surgery, which therefore is an explanatory factor for the increased risks.[86]

In EC, age is a known independent prognostic factor, with decreasing RS with increasing age.[87] Age-specific 5-year RS in Sweden is >90% in the age group <60 years, 87% in the 60–69-year, 81% in the 70–79-year, and 68% in the 80–89-year age group.[88] Elderly women are at increased risk of having a tumor with high-risk histology. In older women, the tumor is more often upstaged after surgery than in younger women and, consequently, staging is important to adequately plan further treatment. Conventional laparoscopic surgery has been shown to be feasible and hence this technique is recommended for primary surgery also in elderly women.[89] Still, MIS is performed less often in elderly women, without obvious reasons.[87, 90]

## 1.11 Summary

The population of women diagnosed with EC and in need of primary surgery is increasing globally. As this is a group of possibly frail patients because of age and obesity, optimal treatment standards are important to reduce risks of complications and mortality. The use of robotic surgery for primary treatment of EC has become the gold standard at many settings – however, without convincing high-level evidence supporting its superiority over other surgical modalities for this diagnosis. Adequate long-term follow-up of selective cohorts of obese and elderly patients after robotic surgery is scarce. Furthermore, as this is a diagnosis associated with favorable long-term prognosis, HRQoL becomes important. Longitudinal follow-up of these aspects in EC survivors is needed.

# 2. Aim

The overall aim of this thesis was to evaluate robotic surgery in women undergoing primary treatment for EC, with regard to surgical outcomes, costs, survival, and HRQoL.

*The specific aims were:*

**Paper I**

- To compare robotic surgery to open surgery in women with EC, with regard to surgical outcomes, costs, and return to activities of daily living (ADLs)

**Paper II**

- To compare elderly patients undergoing surgery for EC, before and after the introduction of robotic surgery, with regard to long-term survival, surgical outcomes, and costs

**Paper III**

- To compare long-term survival, recurrence, and postoperative complications in obese patients with EC, undergoing robotic or open surgery

**Paper IV**

- To describe HRQoL in women undergoing robotic surgery for EC

# 3. Patients and Methods

Patient cohorts and the study design of the papers included in this thesis are summarized in Table 3.

**Table 3.** Overview of the included papers (I-IV)

| Variables | Paper I | Paper II | Paper III | Paper IV |
|---|---|---|---|---|
| **Type of study** | Prospective observational cohort | Retrospective observational cohort | Retrospective observational cohort | Prospective observational cohort |
| **Number of participants** | 88 (40/48) | 278 (141/137) | 217 (131/86) | 64 |
| **Setting** | WSHCR | SUH | SUH | SUH |
| **Treatment** | Robotic/open surgery | Robotic/open surgery | Robotic/open surgery | Robotic surgery |
| **Period of inclusion** | Sept 2010-Dec 2012 | 2006-2009 + 2011-2014 | 2006-2009 + 2011-2014 | June 2019-June 2020 |
| **Source of information** | Surgical administrative system, medical files, PROs by telephone interviews | Surgical administrative system, medical files, Swedish Population Register | Surgical administrative system, medical files, Swedish Population Register | PRO questionnaires: EORTC QLQ-C30 + EN24, GAD-7, PHQ-9 |
| **Outcomes** | Surgical, health care costs, PROs (return to ADLs) | Surgical, health care costs, RS, OS | Surgical, RS, OS - adjusted, DFS - adjusted | PROs: HRQoL, depressive and anxiety symptoms |

ADLs=activities of daily living; DFS=disease-free survival; EN24=Quality of life Questionnaire Endometrial cancer 24; EORTC=European Organization for Research and Treatment of Cancer; GAD-7=General Anxiety Disorder Assessment; HRQoL=health-related quality of life; OS=overall survival; PHQ-9=Patient Health Questionnaire 9; PRO=patient-reported outcome; QLQ-C30=Quality of Life Questionnaire Core 30; RS=relative survival; SUH=Sahlgrenska University Hospital; WSHCR=Western Sweden Health Care Region

## 3.1 Setting

The studies were performed in the Western Sweden Health Care Region (WSHCR), with a population of 1.9 million. Sahlgrenska University Hospital (SUH) is the university hospital and tertiary setting in the region; in addition, there are four county hospitals. The SUH has subspecialists in gynecological oncological surgery, performing all types of gynecological surgeries including robotic surgery. The Gynecologic Oncology Department has regional responsibilities for all medical oncological protocols including chemo- and radiotherapy and targeted therapies. During the study period, approximately 140 patients per year underwent surgery for EC at SUH, and the numbers have increased over the last years.

## 3.2 Study population

All patients included in the studies had a diagnosis of EC, presumed FIGO stage I–II, histologically confirmed by a reference specialist in gynecologic pathology. During the study period, when the majority of the patients described in Papers I–III underwent surgery (2006-2013), a regional guideline for management of EC was in use (see above), including a risk classification, and identification of patients to be recommended for systematic pelvic lymphadenectomy (Fig 4). By the end of the last year of that study period (2014), the first Swedish NGEC had been implemented, recommending patients with high-risk preoperative tumors to undergo systemic PPLND. In the robotic group in Paper III, six patients underwent the PPLND procedure. Patient and tumor characteristics for patients reported in Papers I–III are summarized in Table 4, showing updated information with homogenous descriptive statistics, to complement Table 1 in each of Papers I–III. Patients planned for robotic surgery, who were subsequently converted to open surgery, were kept in the robotic groups in an intention-to-treat analysis, throughout the studies.

### *Paper I*

In Paper I, patients were prospectively included and allocated to a surgical modality based on the hospital where they were to receive treatment. Patients were included from September 2010 until December 2012. At that time, the robotic system had been introduced at SUH and was the surgical modality of choice for EC. At the regional county hospitals, no robotic system was available and, hence, gynecologic surgeons were limited to open surgery when performing lymphadenectomy. All patients in this cohort had risk factors recommending pelvic lymphadenectomy (Fig 4). The sample size in Paper I was restricted by the fact that a new national guideline was about to be introduced (implementation process in 2013), changing recommendations for lymphadenectomy according to the NGEC. Hence, inclusion was stopped by the end of 2012.

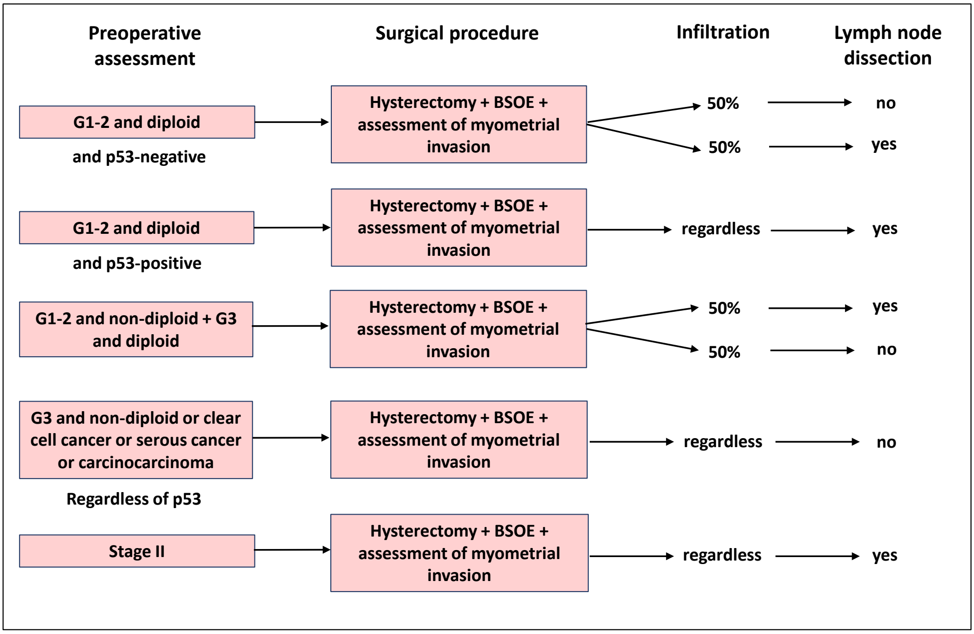


**Figure 4.** Guideline for assessment and treatment of tumors, regarding pelvic lymphadenectomy. Adapted from the regional guidelines 2005[63]

BSOE=bilateral salpingo-oophorectomy, G=grade

## *Papers II and III*

In the studies reported in Papers II and III, patients treated for EC at SUH in 2006-2009 and again in 2011–2014 (at the time when robotic surgery was introduced) were included based on age (Paper II) and BMI (Paper III), and identified through the hospitals surgical administrative system. Patients underwent hysterectomy, BSOE and additional staging procedures according to the guidelines. In 2010, the Da Vinci® system was introduced at the Department and that year was excluded to reduce bias due to selection between surgical method and possible surgical inexperience. Since 2011, robotic surgery has been the method of choice, irrespective of age or BMI, at our institution. However, during the study period, approximately 60% of all patients undergoing surgery for EC were treated by robotic surgery. Constraints in robotic capacity meant that the proportion was kept at this level. Hence, patients undergoing robotic surgery in 2011-2014 were compared to those undergoing open surgery during 2006–2009, before the introduction of robotic surgery. Frail patients, such as elderly and obese patients, were clinically perceived to benefit from the robotic method and therefore largely allocated to robotic surgery (surgeons' personal experiences).

In Paper II, we restricted the cohort to the elderly patients, defined as ≥70 years on the day of surgery. The definition of elderly varies between studies.[91] The age of 65 years has traditionally been used in many settings. In the western world, including Sweden in particular, the age of 65 is today not associated with obvious vulnerability and first in higher ages an increased frailty is seen. Many people still have an active life, including employment at the age of 65 years, why we choose to define elderly as 70 years. The same definition is used in other publications on EC.[91, 92] In Paper III, we restricted the cohort to the obese patients. We defined obesity according to the WHO definition of obesity class I, i.e., BMI ≥30 kg/m$^2$. Among the patients undergoing primary surgery for EC 2006-2009, 27% were obese, and during 2011-2014, 40% were obese.

The two groups compared in each study appear to have been equivalent in most respects (Table 4). In Paper II, it is worth noting that a few patients (3% in the open surgery group and 4% in the robotic group) were classified as having hyperplasia with atypia, and no cancer. This could theoretically affect the survival data, but we have chosen to keep these patients in the study cohort as the recommendation for all women with atypical hyperplasia is surgical treatment, and for other outcomes studied, they should add valid information. There is also a tendency towards more favorable American Society of Anesthesiologists (ASA) score and fewer previous abdominal surgical procedures, in the robotic group, though neither a statistically significant difference.

In Paper III, a statistically and clinically significantly higher rate of high-risk histology was seen in the open surgery group, and accordingly, a higher percentage of patients in this group received adjuvant therapy. There was also a tendency for a higher rate of obesity class III, BMI ≥40 kg/m$^2$, in the robotic group, although this did not reach significance. Some attention can be paid to the distribution of Charlson Comorbidity Index (CCI) (see below) score in this obese cohort, with a rate of only 15.2% having a CCI score ≥2.[93] However, the rate may be considered well balanced between the groups, 16.3% in the open surgery group and 14.6% in the robotic group, with a non-significant difference in overall CCI score.

**Table 4.** Patient and tumor characteristics (Papers I-III)

| | Paper I | | Paper II | | Paper III | |
|---|---|---|---|---|---|---|
| | **Open surgery** | **Robotic surgery** | **Open surgery** | **Robotic surgery** | **Open surgery** | **Robotic surgery** |
| **Number of patients** | n=48 | n=40 | n=137 | n=141 | n=86 | n=131 |
| **Age** (years), median (range) | 67 (44-84) | 66.5 (47-87) | 78 (70-91) | 76 (70-92) | 67 (37-87) | 68 (43-91) |
| **BMI** (kg/m2), median (range) | 28 (19-44) | 28 (19-46) | 27 (18-48) | 28 (17-49) | 34 (30-49) | 36 (30-67) |
| **FIGO-stage***, n (%) | | | | | | |
| Hyperplasia with atypia | | | 4 (3) | 5 (4) | | |
| 1A | | | 90 (66) | 87 (62) | 63 (73.3) | 91 (69.5) |
| 1B | | | 22 (16) | 23 (16) | 10 (11.6) | 19 (14.5) |
| II | | | 6 (4) | 11 (8) | 4 (4.7) | 11 (8.4) |
| III | | | 14 (10) | 13 (9) | 8 (9.3) | 9 (6.9) |
| IV | | | 1 (1) | 2 (1) | 1 (1.2) | 1 (0.8) |
| **Histology****, n (%) | | | | | | |
| Endometroid G1 | 14 (29) | 10 (25) | 21 (15) | 27 (19) | 26 (30.2) | 28 (21.4) |
| Endometroid G2 | 25 (52) | 21 (53) | 51 (38) | 51 (36) | 36 (41.9) | 83 (63.4) |
| Endometroid G3 | 9 (19) | 9 (22) | 20 (15) | 24 (17) | 15 (17.4) | 11 (8.4) |
| Carcinosarcoma | | | 6 (4) | 1 (1) | 4 (4.7) | 2 (1.5) |
| Clear cell | | | 6 (4) | 13 (9) | 2 (2.3) | 1 (0.8) |
| Serous | | | 8 (6) | 10 (7) | 3 (3.5) | 6 (4.6) |
| Not stated | | | 7 (5) | 6 (4) | | |
| **ASA score**, n (%) | | | | | | |
| I | | | 4 (3) | 14 (10) | 8 (9.3) | 18 (13.7) |
| II | | | 91 (66) | 85 (61) | 49 (57.0) | 68 (51.9) |
| III | | | 41 (30) | 41 (29) | 28 (32.6) | 45 (34.4) |
| IV | | | 1 (1) | 0 (0) | 1 (1.2) | 0 (0.0) |
| **Previous abdominal surgery,** n (%) | | | | | | |
| 0 | | | 70 (51) | 85 (60) | 37 (43.0) | 71 (54.2) |
| 1 | | | 43 (31) | 38 (27) | 26 (30.2) | 38 (29.0) |
| ≥ | | | 24 (18) | 18 (13) | 23 (26.7) | 22 (16.8) |
| **Charlson Comorbidity Index,** n (%) | | | | | | |
| 0 | | | | | 53 (61.6) | 86 (65.6) |
| 1 | | | | | 19 (22.1) | 26 (19.8) |
| 2 | | | | | 13 (15.1) | 15 (11.5) |
| 3 | | | | | 1 (1.2) | 3 (2.3) |
| 5 | | | | | 0 (0.0) | 1 (0.8) |
| **Comorbidity,** n (%) | | | | | | |
| None | | | 31 (23) | 31 (22) | | |
| HT | | | 69 (50) | 73 (52) | | |
| Cardiovascular | | | 33 (24) | 25 (18) | | |
| Diabetes | | | 20 (15) | 12 (9) | | |
| Pulmonary | | | 9 (7) | 12 (9) | | |
| Cerebrovascular | | | 14 (10) | 14 (10) | | |
| Thromboembolism | | | 10 (7) | 6 (4) | | |
| Other disease of significance | | | 7 (5) | 32 (23) | | |

ASA=American Society of Anesthesiologists; BMI=body mass index; FIGO=International Federation of Gynecology and Obstetrics; G=grade; HT=hypertension; n=number

* According to FIGO 2009; ** for Paper II this refers to preoperative histology

## *Paper IV*

In the study reported in Paper IV, patients were included prospectively at SUH during 1 year, from June 2019 until June 2020. Patients planned to undergo primary surgery for EC using robotic technique were invited to be included in the study. All patients were planned to undergo hysterectomy, BSOE, and additional staging via robotic surgery. All patients received pre- and postoperative care at the Gynecologic Oncology Surgical Department at SUH. Depending on risk assessment postoperatively, some patients were recommended and given adjuvant treatment, according to the NGEC.[2]

# 3.3 Data collection

*Patient characteristics and surgical outcomes*

For Papers I–III, demographic data were collected from each individual electronic patient file. In Paper I, unfortunately no data on comorbidities were registered. The rationale for reporting on comorbidities is that they can act as a confounder or as an effect modifier. Comorbidities could possibly affect the time of diagnosis to treatment and several outcomes, including prolonged hospitalization, complications, or increased mortality.[94] Different approaches to reporting on comorbidities in standardized ways have been suggested. In Paper II, the ASA classification is used, and in addition, comorbidities are categorized by organ system. In Paper III, comorbidity is summarized using the internationally used Charlson comorbidity index CCI.[93] This instrument was initially presented in 1987, as a method to estimate risk of death due to comorbidity in longitudinal studies. It takes into account both the number of comorbid conditions and their seriousness. The CCI has been widely used in research and is considered a valid tool for measuring comorbidities, particularly in the context of increased mortality due to comorbidity.[94] All comorbid conditions in an individual patient are weighted, and summed to provide the total CCI score.

For Paper I–III, surgical variables and complications were collected from individual electronic patient files and the hospital's administrative system, by two physicians involved in the project. In Paper I, postoperative complications were divided into early (during the hospital stay) and late (within 30 days of surgery). In Papers II and III, the internationally used Clavien-Dindo (CD) classification system was used to classify postoperative complications (Table 6).[95] The system has been developed to standardize the classification of postoperative adverse events, and its grading is based on the intervention needed to treat the complication. To objectivize intraoperative adverse events, we categorized them according to organ system.

**Table 5.** Weight index of comorbidity according to the Charlson Comorbidity Index (CCI)

| Assigned weight | Conditions |
|---|---|
| 1 | Myocardial infarction<br>Congestive heart failure<br>Peripheral vascular disease<br>Cerebrovascular disease<br>Dementia<br>Chronic pulmonary disease<br>Connective tissue disease<br>Ulcer disease<br>Mild liver disease<br>Diabetes |
| 2 | Hemiplegia<br>Moderate or severe renal disease<br>Diabetes with end organ damage<br>Any tumor<br>Leukemia<br>Lymphoma |
| 3 | Moderate or severe liver disease |
| 6 | Metastatic solid tumor<br>AIDS |

AIDS=acquired immune deficiency syndrome

**Table 6.** Classification of surgical complications according to Clavien-Dindo

| Grade | Definition |
|---|---|
| I | Any deviation from the normal postoperative course, without need for intervention (pharmaceuticals for symptom relief excepted, i.e., antiemetics, antipyretics, electrolytes) |
| II | Complication requiring pharmacological treatment |
| III | Complication requiring surgical, endoscopic, or radiological intervention |
| IIIa | Complication requiring intervention not under general anesthesia |
| IIIb | Complication requiring intervention under general anesthesia |
| IV | Life-threatening complication requiring ICU management |
| V | Death |

ICU=intensive care unit

*Cost per patient*

Calculating and comparing health care costs is a challenge, since rarely standardized or consensus methods to perform and report on these analyses are used. Comparing different studies on costs should be done with caution as costs included vary widely. Most regions in Sweden, including the WSHCR, record patient-related costs in the case costing system cost per Patient (**CPP**). This system has been used to record costs per patient in the WSHCR since the mid-1990s. The system aims to calculate actual costs for each individual patient contact with the health care system, rather than estimating standard costs.[96, 97] The case costing system continuously records costs during a patient's hospital visit, based on the patient's individual identification number. The total cost includes all costs at ward care (including medications, radiology, laboratory tests) and all costs for staff, both on the ward and in the operating theater. Additional costs in the operating theater (drapings, single-use only instruments, etc.) are also included. In Papers I and II, the CPP system was used to evaluate costs. Paper I calculated costs for the surgery including all adjacent costs and direct postoperative ward care. In addition to this, in Paper II we also added costs for any subsequent hospitalization 30 days postoperatively, in order to assess complete costs that may be associated with the surgical procedure although not registered during the hospital stay. Paper II spans several years, and consequently we adjusted all costs to the price index for 2015. Additional costs related to investment and maintenance of the robot are based on 350 procedures yearly and a 7-year depreciation of the robotic system.[98]

*Recurrence*

Data on recurrence was collected from each individual patient file throughout the follow-up (truncated at 5 years), ensuring accurate data on recurrences. This data is based on the medical oncologists' evaluation and decisions, as recorded in the patient files.

*Survival data*

In Sweden, all inhabitants are assigned a personal identification number, enabling collection of data by authority registries and enabling research. Data on vital status was ultimately collected from the Swedish Population Register, which ensures lifelong follow-up and provides date of death. The Swedish Quality Register for Gynecological Cancer (SQRGC) for EC was initiated in January 2011, to which data on vital status is daily transferred from the Swedish Population Register. For the study cohort from 2011–2014, vital status was retrieved from the SQRGC. In the earlier cohort, operated in 2006–2009, patients are not included in the SQRGC and instead data on vital status was collected directly from the Swedish Population Register, based on personal identification numbers. Data on vital status was collected on September 26th, 2016, for Paper II and October 29th, 2019, for Paper III.

*Patient-reported outcomes*

In Paper I, systematic interviews performed by telephone were carried out postoperatively to evaluate patients' experiences of treatment and recovery. One single doctor, based at SUH but not performing the surgeries, conducted all the interviews, and the aim was to reach the patients 8 weeks postoperatively. Two questions were asked:

1. *Were you satisfied with the length of time you spent in hospital after your surgery?*
2. *How many days did it take you to regain normal capacity in daily living after the surgery?*

In Paper IV, four validated questionnaires were used to evaluate PROs (Appendix). The questionnaires were distributed at baseline (before surgery) and postoperatively after 2 weeks and 3 months (Fig 5). At baseline, questionnaires were handed to the patient in the ward (after cancer diagnosis, but before surgery) and at the follow-ups, questionnaires were sent by regular mail, accompanied by a prepaid envelope.

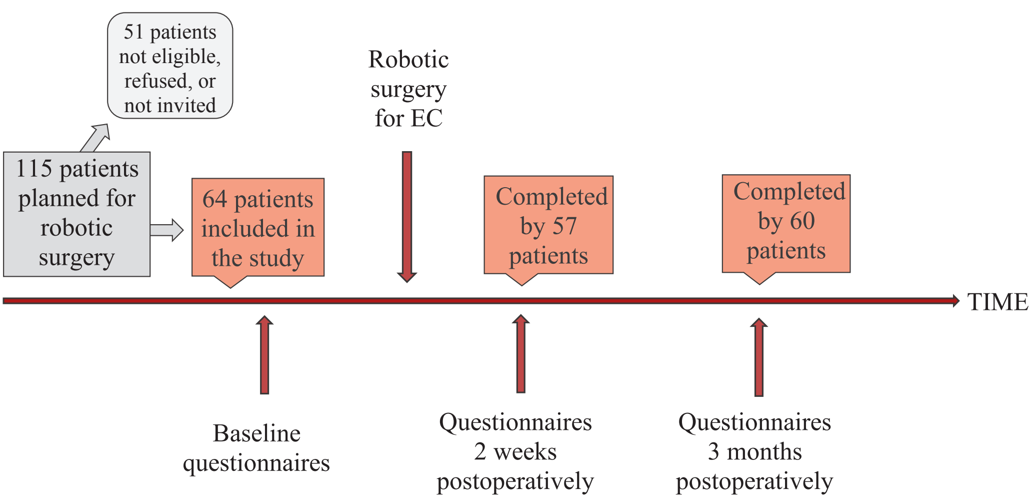


**Figure 5.** Flowchart of patients included in Paper IV

The EORTC has developed a now well known, questionnaire specific for cancer patients, the Quality of Life Questionnaire Core 30 (**QLQ-C30**).[99] It includes overall QoL (global health status (GHS)), five functional scales, three symptom scales and six single items.

The EORTC's complementary module for EC (**EN24**), includes questions related specifically to possible symptoms after treatment for this diagnosis; as well as three functional scales, five symptom scales and five single items.[99] The questionnaires have been validated in Swedish and are considered to have good psychometric qualities. Internal consistency for EN24 with Cronbach's alpha coefficients was ranging from 0.74 to 0.97.[100, 101] In total the EORTCs questionnaires used contains 54 items. Scores are linearly transformed to a 0-100 scale for each scale/symptom, with a high value indication a good HRQoL in the functional scales, and the opposite for the symptom scales. No threshold for absolute scores are commonly used, rather minimally important changes over time in a relative manner, by comparison to previous assessments of the same patient or to other patients groups.[102]

The Patient Health Questionnaire 9 (**PHQ-9**) was developed to be used as a self-administered tool to detect depression. The PHQ-9 contains 9 items, with a total score ranging from 0-27.

The PHQ-9 can be used either to make a diagnosis of probable major depressive disorder or, using cut points 5, 10, 15, and 20, respectively representing mild, moderate, moderately severe, and severe levels of depressive symptoms. The cut point of $\geq$10 is commonly used for clinically significant symptoms of depression.[103, 104] Originally it was tested in studies of over 6000 patients and later its reliability and validity, also in Swedish, was established and shown to be equal or superior to other measures of depression.[105] Psychometric properties have been shown to be good. Psychometric properties for the PHQ-9 have been shown to be good, with an internal consistency in the range (Cronbach's $\alpha$) 0.86-0.89 and a test-retest reliability of $r$ = 0.84.[103] The PHQ-9 has had a significant uptake during the last two decades, both clinically and in research.

The General Anxiety Disorder Assessment (**GAD-7**) was initially developed as a measure to make a probable diagnosis and grade generalized anxiety disorder, but has also been shown to have good sensitivity and specificity as a screener for the other three most common anxiety disorders (panic disorder, social anxiety disorder, and post-traumatic stress disorder).[106, 107] The GAD-7 contains 7 items, with a total score ranging from 0-21. The cut point of ≥10 to detect clinically significant anxiety is often used.[103] The GAD-7 has good internal consistency (Cronback's α) of 0.92 and a good test-retest reliability of $r = 0.83$.[103] Whereas the PHQ-9 can serve as both a diagnostic and a severity measure, the GAD-7 measures the severity of anxiety, with a higher GAD-7 score indicating increased likelihood of an anxiety disorder, although this has to be confirmed by a clinical interview.[103] Both PHQ-9 and GAD-7 have been shown to be valid in the general population.[108, 109]

## 3.4 Statistical analyses

The statistical analyses of observational studies need to be carefully considered, so as not to misinterpret findings. To optimize the quality of analyses, we have been cooperating with professional statisticians in all four papers.

**3.4.1 Sample size and statistical significance**

Defining the sample size needed is an important step in designing a study. Ideally, sufficient number of participants, but not more, should be included to have the statistical power to confirm or reject the hypothesis. For Paper II and III, power calculations were made on the outcome postoperative complications. This was in an early phase, when few publications on obese and elderly were available and the expected postoperative complications after open surgery was set to 20% with a reduction to 8% after robotic surgery, based on prior results.[40, 110] With a power set to 80%, and significant level at 5%, we calculated a required sample size of 150 patients, presuming equal samples. This was expected to be reachable considering the proportion of elderly and obese during 2011-2014. A p-value of $<0.05$ was considered statistically significant throughout the analyses. This has long been considered the accepted gold standard of "statistical insecurity," but may also falsely interpret as "interesting results." Often results not reaching this level of "significance" have been difficult to publish. There are scientists suggesting that there should be more acceptance for interpreting point estimates as most probably true, and evaluating the clinical significance of this, even in the absence of statistical significance ($p \geq 0.05$).[111] However, the misinterpretation that a p-value ≥0.05 indicates that the two exposures are equal may be a concern in medical biostatistics, which should be considered when drawing conclusions from these studies.

### 3.4.2 Descriptive analyses

Based on distribution of data, a fitting statistical test was chosen for each dependent variable. Details on methods used are specified in each paper. For continuous parametric data, Student's *t*-test was used, while Mann-Whitney U test was used in case of non-parametric data. In Paper I, data on estimated blood loss (EBL) were analyzed on the logarithmic scale, which can turn non-normal distributions into normal distributions, allowing for parametric models to be used. To compare categorical variables between groups, chi-square test was used. In some analyses in Paper III, where individual values could be expected to be low, the two-tailed Fisher's exact test was used instead.

### 3.4.3 Survival analyses

For all survival analyses, the follow-up was truncated at 5 years after diagnosis. Patients were followed from the date of their diagnosis (entering the survival analysis) until event (death or recurrence) or until 5 years after diagnosis. The Swedish Population Register enabled us to establish patients' survival time, until potentially censored if patients emigrated before the 5 years' cutoff or until the follow-up was truncated.

**Overall survival** is a measure of total mortality, no matter the cause. This defines the proportion of patients who are alive after a defined period of time. To estimate OS, the Kaplan-Meier method was used.

**Relative survival** is a net survival measure, showing EC survival in the absence of other causes of death. RS is defined as the ratio of the proportion of observed survivors in a cohort of patients with a specific diagnosis (here, EC) to the proportion of expected survivors in an age- and gender-matched group of individuals without the diagnosis. Death rates of the Swedish population were used for the estimation of RS, in Paper II using the Ederer II method and in Paper III using the Pohar-Perme estimator.

**Disease-free survival** describes the period after a successful treatment during which there are no signs or symptoms of the disease that was treated, in this case EC. Disease-free survival was defined as time from diagnosis to first recurrence or death, whichever came first. To estimated DFS, the Kaplan Meier method was used.

### 3.4.4 Multivariable analyses

Different statistical models for multivariable analyses are available. Depending on the distribution of data and the characteristics of the exposure and outcome variables (dichotomized, categorical, or continuous) an appropriate model is chosen. Analysis of the effect of exposures on studied outcomes may reveal associations between the variables that will be interpreted as causal effects, while the real association is a third variable, the confounder. In observational studies, some confounders can be identified, and possibly adjusted for. To estimate the potential effect of surgical modality on OS and DFS in Paper III, multivariable analyses were done to model the relationship between different confounders and hazard rates, using a Cox regression model. In Paper IV, the association between GHS at 3 months and different patient characteristics was analyzed using linear regression models. Furthermore, in order to find the strongest associations, a multivariable linear regression analysis was performed using stepwise selection method on variables univariably significant at $p < 0.1$.

## 3.5 Ethical permissions

Ethical approval was obtained from the regional ethical review Board of Gothenburg for the four papers in this thesis. Paper I reg number: 594-09 and Paper II-IV: 874-15.

Women in Paper I and IV gave their written and informed consent, and could withdraw at any time. All data was collected and handled by authorized personnel. Once included, every patient was given a unique anonymous identification code.

# 4. Results and comments

In this section, results from this thesis are summarized and discussed by outcome, rather than by the individual papers.

## 4.1 Surgical outcomes

- Operative time was equivalent between the two surgical modalities in the elderly cohort (Paper II), and shorter for robotic surgery in the two other cohorts (Paper I and III). Hence, in this setting, the results for operative time did not show to be longer for robotic surgery.

- The rate of conversions was low in both the elderly and the obese cohort, 3% and 4.6%, respectively.

- EBL was shown to be significantly lower during robotic surgery in all three papers.

- The postoperative length of hospital stay after robotic surgery was found to be statistically and clinically significantly shorter in all included cohorts.

Surgical outcomes and estimated 5-year survival are summarized in Table 7.

*Comments*

Results for EBL and length of hospital stay were in favor of robotic surgery throughout the papers. This is in line with what has been described previously for the technique, and it is reassuring to see that this is true also for obese and elderly patients. Surgical outcomes after robotic surgery have been extensively studied in observational studies, and in a few RCTs.[43, 45] The reduction in blood loss seen with robotic surgery is probably a result of precise dissection. With the excellent three-dimensional vision provided by the robotic camera, even small vessels come into sight and can be diathermized. In all laparoscopic surgery, adequate vision is of paramount importance, probably in addition contributing to surgeons' careful surgical dissection and thorough peroperative coagulation. Reduced blood loss may seem of insignificant importance, but bearing in mind that many patients with EC are at increased risk of other complications due to obesity and age, it could be crucial.

Shorter length of stay may have several explanations, including faster physical recovery after robotic surgery, which is largely understood as a benefit of reduced abdominal trauma. Possibly there is an indirect effect from reduced use of analgesics. The advantages of reduced length of hospital stay are several. Reduced hospital stay is known to reduce the risks for complications associated with inpatient care, such as nosocomial infections. Obviously, there is a potential to cut costs when admissions are kept shorter. In addition, elderly patients, who constitute a large portion of these patients, are known to be vulnerable to fall and cognitive problems when taken away from their home environment. The benefits of early discharge from the hospital after surgery are strengthened by the satisfaction with the length of hospital stay reported by the patients in Paper I, as previously mentioned.

From the results in this thesis, we conclude that, with experienced surgeons, robotic surgery is not associated with longer operative time, compared to open surgery, in contrast to what has been reported in several previous studies including two retrospective comparisons of elderly (≥70 years) and obese (≥30 kg/m$^2$) women undergoing robotic or open surgery for EC.[40, 45, 92, 112] In two of the three papers reporting operative time in this thesis, the opposite is shown, with a reduced operative time for robotic surgery. However, total occupation of operating theater and anesthesia time are shown to have been longer for robotic surgery in Paper II. This is of interest, and should be investigated further since this drives costs and ultimately affects the efficient use of the robotic surgical systems. Differences in operative time, in the different publications, may have several explanations. One possible factor is selection bias, disqualifying patients with foreseen complicated surgeries from the robotic modality in some setting. In our material, we know that robotic procedures were performed by surgeons highly experienced in both open and robotic surgery, which may possibly be reflected in generally favorable operative times.

**Table 7.** Summary of surgical outcomes and estimated 5-year survival for Papers I-III

| | **Paper I** | | | **Paper II** | | | **Paper III** | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Open surgery** n=48 | **Robotic surgery** n=40 | **p-value** | **Open surgery** n=137 | **Robotic surgery** n=141 | **p-value** | **Open surgery** n=86 | **Robotic surgery** n=131 | **p-value** |
| **Operative time** (min), median (range) | 175.5 (97-306) | 127.5 (68-195) | <0.0001[a] | 97 (37-287) | 93 (43-304) | 0.704[a] | 108.5 (51-287) | 98 (44-315) | 0.032[b] |
| **Anesthesia time** (min), median (range) | | | | 166 (93-361) | 173 (92-406) | 0.045[a] | | | |
| **Operating theater time** (min), median (range) | | | | 179 (109-376) | 191 (104-421) | 0.011[a] | | | |
| **Estimated blood loss** (ml), median (range) | 250 (50-1100) | 50 (10-200) | <0.0001[a] | 250 (0-4000) | 25 (0-400) | <0.001[a] | 250 (20-2500) | 25 (5-2000) | 0.001[b] |
| **Intraoperative complications,** n (%) | | | | | | 0.139[c] | | | 0.559[d] |
| None | | | | 136 (99.3) | 135 (95.7) | | 86 (100) | 126 (96.2) | |
| Vessel injury | | | | 1(0.7) | 0(0) | | 0 (0) | 0 (0) | |
| Bowel injury | 1 | | | 0 (0) | 2 (1.4) | | 0 (0) | 2 (1.5) | |
| Urinary Tract injury | 1 | 2 | | 0 (0) | 3 (2.1) | | 0 (0) | 2 (1.5) | |
| Other Organ injury | | | | 0 (0) | 1 (0.7) | | 0 (0) | 1 (0.8) | |
| **Conversions,** n (%) | NA | 0 (0) | | NA | 4(2.8) | | NA | 6 (4.6) | |
| **Lymph node removal** | | | | | | 0.714[c] | | | 0.345[c] |
| No | | | | 110 (80.3) | 109 (77.3) | | 75 (87.2) | 108 (82.4) | |
| Yes | 48 (100) | 40 (100) | | 27 (19.7) | 32 (22.7) | | 11 (12.8) | 23 (17.6) | |
| **Length of hospital stay** (days), median (range) | 4 (2–11) | 1 (1–5) | <0.0001[b] | 5 (2–28) | 2 (1–36) | <0.001[a] | 5 (2–22) | 1 (1–36) | 0.001[b] |
| **Postoperative complications (***Clavien Dindo)* | | | | | | 0.109[c] | | | 0.032[d] |
| None | | | | 95 (69.3) | 115 (81.6) | | 61 (70.9) | 110 (84.0) | |
| I | | | | 6 (4.4) | 5 (3.5) | | 2 (2.3) | 2 (1.5) | |
| II | | | | 30 (21.9)) | 14 (9.9) | | 19 (22.1) | 12 (9.2) | |
| III | | | | 5 (3.6)) | 4 (2.8) | | 3 (3.5) | 7 (5.3) | |
| IV | | | | 0 (0) | 2 (1.4)) | | | | |
| V | | | | 1 (0.7)) | 1 (0.7) | | 1 (1.2) | 0 (0) | |
| **Overall 5-year survival,** % (95%CI) | | | | 69 (62-78) | 77 (68-86) | | 75.6 (67.0-85.2) | 87.0 (81.5-93.0) | |
| **Relative 5-year survival,** % (95%CI) | | | | 87 (78-98) | 94 (84-105) | | 81.6 (72.1-92.3) | 96.2 (89.7-103.3) | |

a=Student's t-test; b=Mann-Whitney; c=Chi-squared test; d=Fisher's exact; CI=confidence interval; NA=not applicable

# 4.2 Complications

- In obese patients, the overall rate of postoperative complications was lower after robotic surgery. Specifically, there was a relative risk of 0.54 (95% CI 0.31–0.93) of getting a postoperative complication of CD grade II–V (a complication that needs intervention) after robotic surgery, compared to open surgery.

- In elderly patients, no significant difference was seen for postoperative complications overall, but there was a reduction in CD grade II complications after robotic surgery, 10% vs 22% (p=0.006).

- Intraoperative complications were not found be more common in either surgical modality, but they are generally few and hence the significance of this finding can be questioned.

In table 8, a specification of the complications, CD grade II-V, in the elderly and obese patients respectively, are presented.

**Table 8.** Number and characteristics of CD complications II-V specified for Paper II and III

| | Elderly – Paper II | | Obese – Paper III | |
|---|---|---|---|---|
| | Open surgery n=137 | Robotic surgery n=141 | Open surgery n=86 | Robotic surgery n=131 |
| CD II | UTI: 11<br>Wound infection: 6<br>Blood transfusion: 6<br>Pulmonary embolism: 2<br>Atrial fibrillation: 3<br>Pneumonia: 1<br>Neurological pain: 1 | UTI: 4<br>Wound infection: 1<br>VV infection: 4<br>Blood transfusion: 1<br>Atrial fibrillation: 3<br>Infection NS: 1 | UTI: 5<br>Wound infection: 8<br>Blood transfusion: 5<br>Pulmonary embolism: 1 | UTI: 3<br>Wound infection: 4<br>VV infection: 2<br>Blood transfusion: 1<br>Bleeding from VV – conservative: 1<br>Heart failure: 1 |
| CD IIIa | Wound complication: 1 | | | Sutures due to port bleeding (in LA): 2<br>Drainage of intraabdominal abscess: 1 |
| CD IIIb | Wound complication: 1<br>Ileus: 2<br>Ileocecal resection: 1 | Intraabdominal bleeding: 1<br>Drainage of VV: 1<br>Vesicovaginal fistula: 2 | Wound complication: 3 | Bleeding from VV: 2<br>Ileus: 2 |
| CD IV | | Aspiration at reoperation – ICU admission: 1<br>Pulmonary embolism – ICU admission: 1 | | |
| CD V | Pulmonary edema (possibly due to AMI) leading to death: 1 | ASA 3 with dialysis preop, deteriorated general condition postoperatively leading to death: 1 | Suspected stroke – death at home: 1 | |

AMI=acute myocardial infarction; ASA=American Society of Anesthesiologists; CD=Clavien Dindo classification; ICU=intensive care unit; LA=local anesthesia; NS=non-specific; Preop=preoperatively; UTI=urinary tract infection; VV=vaginal vault

*Comments*

Our main finding regarding complications is the reduced rate of postoperative complications in obese patients after robotic compared to open surgery. Taken together, the studies included show that surgery for EC is associated with generally low complication rates, but the results are unable to show a difference in overall postoperative complications between the surgical modalities in the complete cohort of this thesis. The rate of CD grade II complications was lower for robotic surgery in both elderly and obese patients, and the difference in CD grade II–V complications seen in the obese patients was mainly a difference in CD grade II complications. Grade II complications require pharmacological treatment. They will in most cases not lead to life-threatening conditions or long-term sequelae for the patients, but could be serious because they include thromboembolic events and pneumonia. However, postoperative complications of this severity do cause prolonged admissions and increased costs, as well as driving antibiotic resistance and, foremost, increased suffering for the already affected patients. Interestingly, more severe postoperative complications, CD grade III-V, were rare, and hence a significant difference was hard to prove. The number of patients undergoing reoperation or in need of intensive care is sporadic after both surgical modalities. Interpreting these results, one should keep in mind that the rates of lymphadenectomies was fairly low in our material, compared to many international publications.

Postoperative complications have in many reports been shown to be reduced, favoring robotic surgery compared to open surgery (Table 10).[40, 53] The RCT by Salehi et al. in 2017 did not show a statistically significant difference in postoperative complications between the modalities.[45] Results from this thesis, however, indicate a benefit after robotic surgery, also for obese and elderly patients.

The reduced surgical trauma is theoretically thought to reduce complications. Lavoue et al. reported a similar reduction in mild complications, CD grade I-II, in a cohort of elderly (≥70 years) patients undergoing open or robotic surgery.[92] Moreover, Guy et al. published a large US register-based study comparing younger and older patients undergoing open or robotic surgery for EC.[43] They reported reduced surgical and medical postoperative complications in those aged ≥65 years, after robotic compared to open surgery. Though having the drawbacks of being a fully register-based study, Guy et al. illustrated how the risk for postoperative complications increased with every 5-year increase in age after 65. From the well-powered randomized LAP2 trial, an interesting retrospective analysis of postoperative complications by age was published in 2018. In the open surgery cohort, an increase in complications was observed at 60 years of age – the reason this was used as the cutoff in the publication. Regarding complication rate for any postoperative complication, patients ≥60 years undergoing open surgery had a rate of 24.5% vs 15.9% in the MIS group, adjusted OR 1.71 (95% CI 1.31-2.25).[113]

In obese patients, a reduction of postoperative complications after MIS has been reported by several authors (Table 10). In ancillary data from the LAP2 trial, postoperative adverse events were reduced after MIS compared to open surgery and increased in general with increasing BMI.[114] Our results, after robotic surgery in obese patients, are strengthened by other retrospective analyses comparing robotic surgery and open surgery in patients with BMI ≥30, 35 and 40 kg/m$^2$, respectively.[48, 112, 115] They all reported a reduction in postoperative complications after robotic surgery, but did not use a standardized classification system for complications. Although, worth noting, was an increase in vaginal cuff dehiscence after robotic surgery, as reported by Tang et al.[112] In our material, we did not see any vaginal cuff dehiscence. This is however not surprising, considering the follow-up time of 30 days. Vaginal cuff dehiscence is a known complication to robotic hysterectomy, with an incidence rate of 1,64% and mean time to presentation 68.5 days, according to a recent metaanalysis.[116] Studies are trying to identify possible risk factors to overcome, aiming at reducing dehiscence.[116] In the light of this, but in general regarding complications, a prolonged follow-up of e.g., 90 days, could be interesting. That will however, introduce possible complications caused by adjuvant therapy, and results hard to interpret. Comparing frequencies of postoperative complications between different publications is difficult when standardized definitions of complications have not been used. In addition, the heterogeneity of studied cohorts present in clinical trials may cause differences. In Papers II and III, we have used CD, which may make our results comparable to others.

## 4.3 Costs

Details on mean costs in Paper I are presented in Table 9. When costs for investment and maintenance of the robotic system are not included, the mean cost for a robotic procedure was 12 286 USD. The mean total cost for open surgery was 15 538 USD.

**Table 9.** Breakdown of mean costs for procedures, 2010–2012 (Paper I)

| | County hospitals (mean of the three) - open surgery | University hospital - robotic surgery | Statistics |
|---|---|---|---|
| Cost/minute in operating facilities | 39.4 | 41.5 | |
| Cost/day for admission to the surgical ward | 870 | 1090 | |
| Disposable material for robotic surgery | | 1701 | |
| Investment costs/procedure for robot | | 958 | |
| Maintenance cost/procedure for robot | | 402 | |
| Surgery and hospital stay/patient | 15 538 | 12 286 | |
| Total cost | 15 538 | 15 347 | NS* |

All costs are means, given in USD (1 USD=6.51 SEK); NA=not applicable; NS=non-significant
*t-test

In Paper II, costs were similar between the surgical modalities, as shown in Table 2 in Paper II. Results are visualized in an adapted version, here in Fig 6.

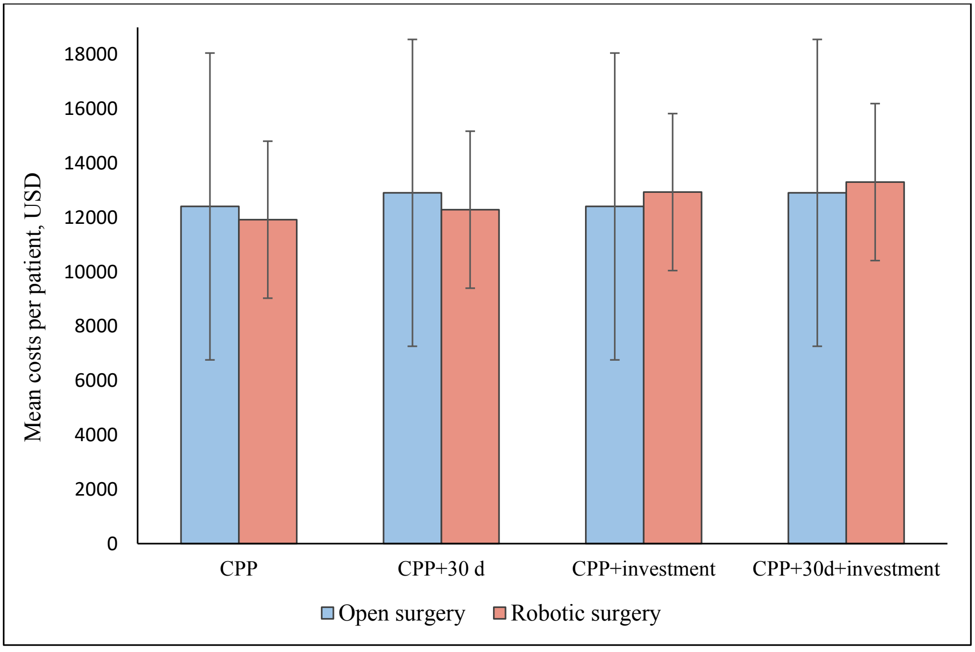


**Figure 6.** Mean cost per patient (CPP) undergoing robotic or open surgery for endometrial cancer (EC) in elderly patients, Paper II. None of the differences were statistically significant 1 USD=8.71 SEK

*Comments*

Findings in Papers I and II indicate that, in high-volume robotic centers, robotic surgery is not more expensive than open surgery even when taking investment costs and complications into account. In the literature, cost calculations have shown diverging results over the years.[47, 117]

In the last years, several publications have shown results, substantiating our findings, where costs for robotic surgery may be equal to, or lower than, open surgery.[118]

There is an RCT from 2017 showing significantly lower costs for robotic surgery (n=48) compared to open surgery (n=48) for EC including pelvic and para-aortic lymphadenectomy (mean costs in USD, including investment (standard deviation (SD)): robotic: 19 937 (4248) vs open: 21 505 (3363), p<0.05).[45] The savings were mainly due to a considerably shorter length of hospital stay after robotic surgery. The surgical procedure in that study is more complex than that commonly reported in other studies from the Scandinavian countries, and hence the costs reflect a different panorama of intra- and postoperative care.

A recent Danish analysis from 2019 showed no reduced costs for those undergoing robotic surgery, compared to conventional laparoscopy or open surgery. When adjusted for time trend, the number of days in hospital was not reduced after robotic surgery.[119] These results could call our analyses regarding costs, with significantly reduced length of hospital stay a factor for cost efficiency in the robotic group, into question as the groups in Paper II were treated in separate time periods.

## 4.4 Survival and recurrence

- Overall survival and RS for the elderly patients did not show a significant difference between the surgical modalities.

- In the obese cohort, the estimated 5-year OS for the total cohort was 82.5%. Table 7 shows 5-year OS divided by surgical modality.

- Overall survival and RS for obese patients was statistically significantly higher after robotic surgery in the survival curves during the 5-year follow-up time. The same trend was seen for DFS, but did not reach statistical significance (Paper III, Fig 3).

- For estimated 5-year OS and DFS, surgical technique was not an independent prognostic factor in multivariable analyses, after adjusting for age, FIGO stage, and histologic risk group, Fig 7 a and b. After adjustment, only histological risk classification remained an independent prognostic factor for both OS and DFS.

The total number of deaths during the follow-up, truncated at 5 years, was in the elderly cohort 42 after open surgery and 26 after robotic surgery (Paper II). In the obese cohort the number of deaths were 21 after open surgery and 17 after robotic surgery (Paper III).

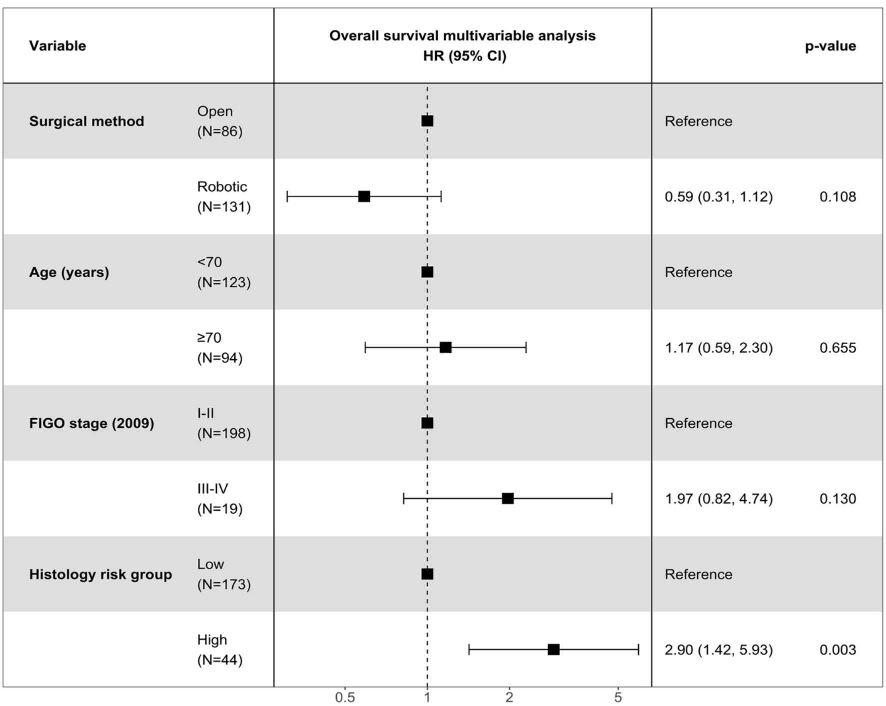


**Figure 7 a.** Forest plot of the multivariable Cox regression analysis, with overall survival (OS) as endpoint
CI=confidence interval; HR=hazard ratio

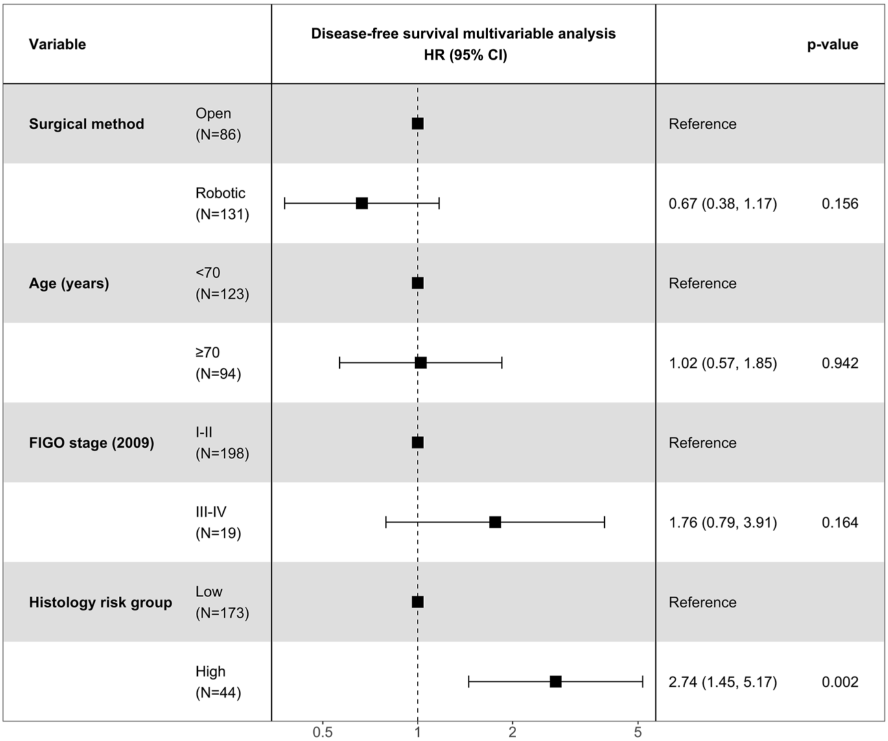


**Figure 7 b.** Forest plot of the multivariable Cox regression analysis, with disease-free survival (DFS) as endpoint
CI=confidence interval; HR=hazard ratio

Specifics on location of recurrences by surgical modality in the obese cohort (Paper III) are shown in Fig 8 a and b.

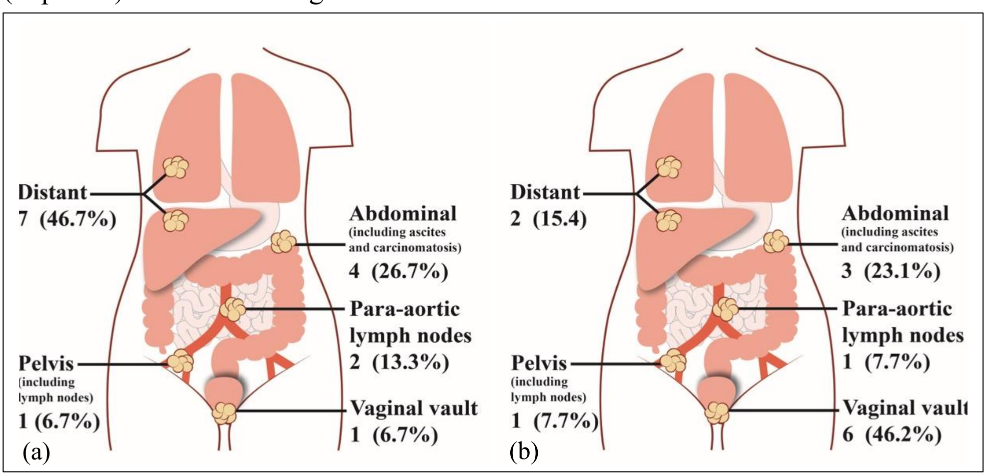


**Figure 8.** Location of recurrences after (a) open surgery; and (b) robotic surgery
*Illustrations by Jan Funke*

*Comments*

Our results on long-term survival trended better for robotic surgery both in the elderly and in the obese cohort. In the elderly cohort, the difference in OS and RS was, however, not statistically significant, while in the obese cohort, the favorable results seen for robotic surgery in OS and DFS disappeared after adjustment for possible confounders. Taken together, the long-term results indicate a similar outcome between the two modalities for these cohorts.

Park et al. in 2015 published data from a single-institution study based on chart reviews (Table 10).[53] The estimated 5-year progression-free survival was 83.0% for robotic surgery vs 75.2% for open surgery (p=0.0003). Further, in adjusted analyses surgical modality was not an independent prognostic factor for recurrence or OS. These results resemble the results in our obese cohort. Park et al. had a higher rate of tumors with less favorable histopathology in the open surgery group, as did we in the obese cohort in Paper III, possibly accounting for the increased survival seen in the survival curves for robotic surgery in both studies.

Furthermore, Jørgensen et al. published a Danish register-based study in 2019, where they compared OS before and after the introduction of robotic surgery, including open surgery and conventional laparoscopy (Table 10).[52] They present two different analytical approaches, and in both, 5-year OS was in favor of robotic surgery. With the Danish population and health care system resembling the Swedish, these results may represent a situation that is transferable to the Swedish EC cohort.

Specifically, regarding elderly women, Wright et al. published a register-based observational study comparing patients aged ≥65 years, where approximately 62% of patients in the MIS group underwent robotic surgery after it was introduced (Table 10).[33] In propensity score-balanced groups, they showed no differences in HR for overall or cancer-specific death between the surgical modalities.

Interestingly, in the Danish study mentioned earlier, a subgroup analysis of “frail” women was done, defined as at least one of the following: advanced age (≥80 years), ASA score III or higher, CCI score ≥II, or women with low/intermediate socioeconomic class.[52] This group, in the absence of selected elderly cohorts, could be compared to our elderly cohort. In this selected cohort, they reported a significantly lower OS in patients treated before the introduction of robotic surgery (HR 1.23 (95% CI 1.04–1.45)), as well as for those undergoing open surgery compared to robotic surgery after the introduction of the new technique (HR 1.65

(95% CI 1.25–2.19)). For the non-frail subgroup, no such difference between periods or surgical modality was seen. This may indicate that robotic surgery is beneficial for EC patients in general and for those considered frail, including elderly patients, in particular.

Survival data in obese patients are scarce. Hinshaw et al. published an observational chart review of 136 patients with obesity class II (BMI ≥35) (Table 10).[115] Their primary outcome was postoperative complications and other surgical outcomes; however, they stated that DFS and OS trended better in the robotic group, though this did not reach significance. The lack of statistically significant differences between the modalities in many studies may be a result of lack of power, due to small sample sizes relative to the rare events of death and recurrence.

In contrary what could be expected, our analyses did not show age and FIGO stage to be independent prognostic factors. Considering the point estimates and CI for FIGO III-IV, the lack of statistical significance is possibly a type II error, for both OS and DFS. Age, by nature should have impact of OS over time, disregarding the diagnosis itself. In EC, where age is a known risk factor for high-risk disease, we would expect to see worse outcomes both in OS and DFS in the higher age group. No obvious conclusion for these unexpected results can be drawn. To some extent, it is possible that the high life-expectancy in Sweden contributes. Further, if we had a sub analysis of the obese women ≥70 years old, any unexpected findings in their tumor characteristics could add explanation.

Specific locations of recurrences are rarely presented as this parameter is hard to obtain and validate. Location is not regularly registered in cancer registries. We have chosen to present the pattern of recurrences in a descriptive manner only, since the overall rates are low and any differences in location may have been only random. The overall 5-year recurrence rate of 12.9% is consistent with the literature.[29] However, we observed in this cohort, a higher rate of vaginal metastasis after robotic surgery and a higher rate of distant metastasis after open surgery. This may have been due to the higher rate of high-risk histology in the open group, rather than to surgical modality, as described in the literature.[120] Site of recurrence has been shown to correlate with survival rate, with distant metastasis being less favorable.[121]

# 4.5 Patient-reported outcomes

In Paper I, 97% of robotic surgery patients and 95% of open surgery patients experienced their length of hospital stay as adequate, while a significant difference between the modalities was seen regarding return to normal ADLs, with a median of 3 vs 14 days in favor of robotics.

In Paper IV, GHS was significantly decreased 2 weeks after surgery, but was back to baseline levels at 3 months' follow-up. Of interest also is the increased emotional and cognitive function seen at 3 months, compared to baseline and 2 weeks postoperatively. Unemployment, low income, and receiving adjuvant therapy were all correlated with lower GHS at 3 months, and the combination of being unemployed and receiving adjuvant therapy may account for a substantial decrease in patients' GHS, according to the multivariable regression model.

Mean scores on GAD-7 and PHQ-9 were fairly low throughout the study, with mean values around 5 at baseline, and then slightly decreasing without clinically significant relevance. The number of patients scoring above the threshold level for clinical assessment (≥10) on GAD-7 showed a clinically and statistically significant decrease from baseline to 2 weeks and remained stable at 3 months. Regarding the number of women reporting symptoms above clinical threshold for depression there were no significant change over the three months. Fig 9 presents the number of patients scoring <10 and ≥10 on the two questionnaires.

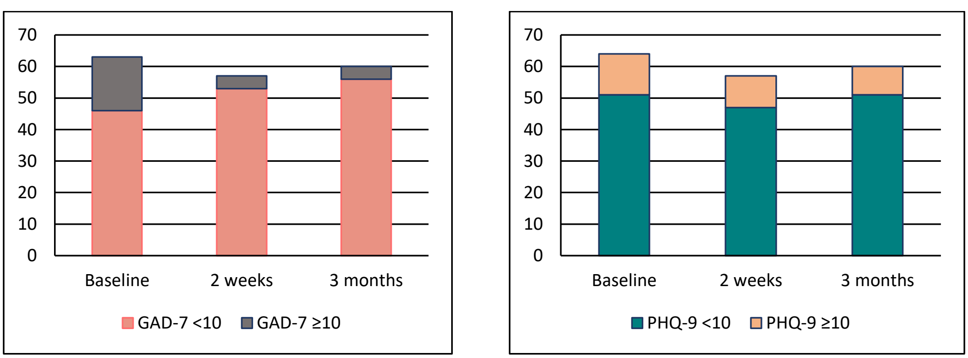


**Figure 9.** Number of patients scoring below and above the clinical threshold of ≥10 on the General Anxiety Disorder Assessment (GAD-7); and the Patient Health Questionnaire 9 (PHQ-9) at different time points. The change from baseline to 2 weeks and 3 months was statistically significant for GAD-7 scores, but not for PHQ-9 scores

*Comments*

Results from PROs in Paper IV indicate that there is no obvious change in HRQoL at 3 months after robotic surgery for EC. The comparison is, however, based on preoperative symptom levels and hence we have no information on these patients' HRQoL before receiving the diagnosis. Comparing our results to norm data in the general population indicates, however, that levels of GHS pre- and postoperatively in this cohort were well in concordance. In a large systematic international study aiming to facilitate a valid comparison of EORTC QLQ-30 results, the GHS in the Swedish general population was reported to be 69.2 (SD 22.1).[122] The same trend of an initial decrease in GHS and later return to baseline levels, or beyond, has been reported in two other longitudinal follow-ups of EC patients who underwent robotic surgery.[123, 124]

The reduction in anxiety symptoms, seen after surgery, may be associated with the emotional stress, caused by the diagnosis itself and by the period of awaiting surgery, which reduces with time and once the surgery is completed. An Italian longitudinal follow-up of 2 years strengthens these results, showing reduction of anxiety scores from baseline to 3 months that persisted throughout the follow-up.[125] Our findings of reported symptoms of depression are more multifaceted. After surgery, increased emotional and cognitive function is stated but still no significant changes in symptoms of depression occurs. This may indicate that the symptoms of depression are more stable over time and less evoked by the diagnosis and surgery.

Moreover, the results from our regression model could be questioned as few patients had the individual variables low income and unemployment. The association with socioeconomic factors has been seen in other studies, however, and should be taken into consideration when counseling patients and designing new studies.[126] The decrease in GHS seen in patients receiving adjuvant therapy is not surprising. These treatment modalities are associated with side effects, of different magnitude, in all patients and with a disease with higher risk of recurrences likely to affect psychological wellbeing.

In Paper I, return to normal ADLs is faster after robotic surgery than open surgery, and a similar difference in HRQoL between the modalities has been shown by others and recently in an RCT by Lundin et al.[127]

**Table 10.** Studies on long-term survival and complication outcomes, after robotic and open surgery, for endometrial cancer, central for this thesis.

| **First author & year of publication** | **Sample size** Robotic/open when not stated other | **Period of study** | **Study design** | **Follow-up** | **BMI (kg/m²)** | **Age (y)** | **Outcome** 95%CI given in brackets |
|---|---|---|---|---|---|---|---|
| Backes[128] 2016 | 89/ 93 | 2003–2009 USA | RS, MC | NS | All | ≥70 | OR Wound dehiscence: 7.6 (1.9-51), readmission: 1.3 (0.53-3.01), reoperation: 3.0 (0.61-22) |
| Boggess[40] 2008 | 103/138 | 2000–2007 USA | PSO with RS control group | NS | All | All | Robotic vs Open: Overall PoCs: 4.9% vs 28.9%, p <0.0001 |
| Chan[48] 2015 | 422/567 | 2011 USA | RB, MC | Direct postop hospitalization period | ≥40 | All | Open vs Robot: Surgical Cs OR: 2.77 (1.75-4.37) |
| Eoh[129] 2020 | 315/1503 | 2012–2016 Korea | RB, nation-wide | NS | All | All | Robotic vs Open: 5-y OS: 94.8% vs 86.9 %, p <0.001 HR Overall death: 0.30 (0.15-0.60) |
| Guy[43] 2016 | 1228/5914 | 2008–2010 USA | RB, MC | Direct postop hospitalization | All | ≥65 | Open vs Robotic: Periop surgical Cs: 20.5%, vs 8.3%, p <0.001; OR 2.85 (2.31-3.53); Periop medical Cs: 23.3% vs 12.3%, p <0.001; OR 2.17 (1.81-2.60) |
| Hinshaw[115] 2016 | 56/80 | 2008–2013 USA | RS, SC | Robotic: 37 m Open: 60 m | ≥35 | | Robotic vs Open: Deaths from disease: 2 vs 6 PoC: 9 vs 28 (p <0.05) |
| Jorgenssen[52] 2019 | Before intro*: 3091, After: 2563 (1282/712) | 2005–2015 Denmark | RB, nation-wide | 8.8/4.4 y (before/after intro*) | All | All | Before intro* vs after: 5-y OS HR 1.22(1.05-1.42) Open vs Robotic - after intro*: 5-y OS HR 1,7(1.31-2.19) |
| Kilgore[130] 2013 | Robotic: 499 | 2005–2010 USA | RS, SC, no control group | 23 m | All | All | 5-y OS: 88.7% |
| Lavoue[92] 2014 | 113/50 | 2003–2013 Canada | PSO, SC | Robotic: 22.7 m Open: 52.0 m | All | ≥70 | Robotic vs Open: Overall Cs OR: 0.38 (0.19-0.75) 2-y DFS: 86% vs 81%, p=0.61 |
| Mok[131] 2012 | 34/90 | 2008–2009 Singapore | RS | 30 days | All | All | Robotic vs Open: Overall PoC: 8.8% vs 25.6%, p=0.032 |

*Cont.*

*Table 10 cont.*

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Park[53] 2015 | 350/586 | 2001–2012 Canada | RS, SC | Robotic: 30 m Open: 42 m | All | All | Robotic vs Open: 5-y OS: 89.1% vs 79.5% (p<0.001), 3–y PFS: 90.9% vs 78.3% (p=0.001) HR R: 0.88 (0.58-1.32), OS: 0.66 (0.38-1.13) Immediate PoC: 0.14 (0.05-0.40), delayed PoC 0.54 (0.31-0.96) |
| Safdieh[132] 2017 | 23 872/20 113 | 2010–2012 USA | RB, MC | 25 m | All | All | Robotic vs Open: 3-y OS HR: 0.76 (0.68-0.84) |
| Salehi[45] 2017 | 48/48 | 2013–2016 Sweden | RCT | 30 days | All | All | Robotic vs Open: Overall PoC: 23% vs 33%, p=0.36 |
| Tang[112] 2012 | 129/110 | 2005–2010 USA | RS, SC | 6 m | ≥30 | All | Robotic vs Open: Wound Cs: 13.9% vs 32.7, p < 0.001; vaginal cuff Cs 4,7 vs 0%, p=0.032 |
| Wright[33] 2016 | Open: 4139 MIS: 2165 (2009–2011: robotic 62%) | 2006–2011 USA | RB | NS | All | ≥65 | MIS vs Open: HR Overall M:0.89 (0.75-1.04), Cancer specific M: 0.83; (0.59-1.16) Overall Cs: 22.7% v 39.1%; OR 0.46 (0.41 - 0.51) |

BMI=body mass index; CI=confidence interval; Cs=complications; DFS=disease-free survival; EC=endometrial cancer; HR=hazard ratio; MIS=minimally invasive surgery; m=months; M=mortality; MC=multi-center; NS=not stated; Open=open surgery; OR=odds ratio; OS=overall survival; periop=perioperative; Postop=postoperative; PoC=postoperative complications; Preop=preoperatively; PSO=prospective observational; PSO=prospective observational; Pts=patients; R=recurrence; RB=register based; Robotic=robotic assisted laparoscopic surgery; RS=retrospective; SC=single-center; y=years; vs=versus
*Intro refers to introduction of robotic surgery in Denmark

# 5. Discussion

## 5.1 Methodological considerations

The design of a study is of paramount importance for the conclusions that can be drawn from its results. Ideally, outcomes related to efficacy of surgery should be studied in a randomized controlled fashion, to avoid bias that cannot be fully controlled for in other designs. Generally, RCTs on robotic surgery in most fields are lacking, for reasons involving the fact that new surgical techniques are developed and introduced without proper safety studies. This is possibly because they are regarded as an evolvement of already implemented surgical techniques, in this case conventional laparoscopy being translated to robotic surgery. This puts patients and surgeons in a position where preferences of surgical modality make comparable control groups a challenge. Nonetheless, new surgical methods should be properly evaluated and scientifically investigated. Observational studies have certain benefits and constitutes complements to RCTs, including external validity, which gives information of how the technique impacts patients in routine practice. Elderly and those with comorbidities including obese patients, are generally under-represented in RCTs and in research in general. The observational cohort design enables us to gain understanding of outcomes in these prioritized groups.[133]

In Papers I and IV, data was collected prospectively, which is believed to have significance, especially for the PROs. In Papers II and III, data was collected retrospectively, to cover a larger patient material. In these studies, we utilized the "before" and "after robot introduction" situation as a proxy for randomization, where patients before the introduction of robotic surgery underwent open surgery and after the introduction were treated by robotic surgery. Importantly, all study patients in Paper II and III were treated at one tertiary center with specialized surgeons. Patients in Paper I-III were included partly from the same cohort of patients. Subsequently, there will be some patients that are included in more than one of the papers. For the validity of each paper this should be of less importance, but needs to be remembered when weighing the results together.

### 5.1.1 Selection bias

In Paper I, patients in the two comparison groups were included from different health care settings. Patients undergoing open surgery during the study period were treated at one of the three local county hospitals in the health care region. The two surgeons at each county hospital, performing the procedures, are experienced gynecological surgeons, although they have no gynecological oncologic subspecialization as do the surgeons at the teaching university hospital performing all the robotic procedures. This may have affected operative time and risk of complications. Further, local traditions and experience of gynecological surgical patients in the operating theatre and postoperative ward may imply confounding we cannot control for.

At the same time, this design enabled a comparison of two surgical modalities, without utilizing a historical cohort, which encompasses other difficulties mentioned below.

In Papers II and III, patients were referred to either of the two surgical modalities based on time period, i.e., whether the surgery occurred before or after the introduction of robotic surgery. Before robotic surgery was available, open surgery was the gold standard. Since the robotic technique was established this has been the method of choice for most EC patients. Due to limited access to the robotic system, however, some patients still underwent open surgery during this later period, and this constitutes a risk of confounding by indication. The selection of patients with presumed early-stage EC to undergo robotic surgery was basically done randomly, but with priority given to those with increased BMI, when access was limited. We chose not to include patients undergoing open surgery in the later period, which could have been an alternative. Since 2011, the mainstay at our institution has been robotic surgery for EC without signs of extra uterine spread. Still, it may be argued that the earlier period encompasses the "full cohort" of EC patients, including those who were not included in the later period.

Paper IV lacks a detailed analysis of patients not included, there was however an even inclusion during the study period and representative age distribution. Such an analysis would have helped to evaluate possible selection bias in this cohort. It may be speculated that patients' preoperative QoL would affect their willingness to participate, or that health care personnel responsible for inclusion would avoid asking those they perceive as having a lot of comorbidities or psychological concerns. The results in this study need to be interpreted carefully and the findings about HRQoL and anxiety/depression could be used for generating hypothesis for future studies.

As the participating hospitals are public, and are in fact the only existing hospitals in the WSHCR at which gynecological cancer surgery is performed, this should make included patients in all four papers unselected cohorts in terms of socioeconomic factors. Since the beginning of the robotic era, patients have occasionally been referred from the other county hospitals to undergo robotic surgery due to severe obesity, which could have influenced the proportion of obese patients in the robotic groups. Simultaneously, obesity has generally increased in the population during the study period.

### 5.1.2 Information bias

Information bias arises when information on exposure or outcome variables is inadequately collected, not reflecting the true and valid information. In Paper I, the PROs may be subject to recall bias as evaluation of return to normal ADLs was not done continuously. We aimed to reach every patient 8 weeks after surgery, but the time varied from 6 to 12 weeks. Patients may remember incorrectly the time-point when they experienced return to normal ADLs, when asked several weeks later. Also, it is possible that patients are not completely honest in their response, when reporting straight to a physician. To what extent this skewed our results is uncertain, but, ideally, patients' experiences of impaired ADLs should be recorded more continuously and confidentially. Using a standardized questionnaire to evaluate HRQoL and ADLs would further have strengthened the results.

The retrospective design of Papers II and III creates a risk of information bias. Data regarding the surgery, operative time, and EBL are believed to be very accurate, since they are systematically and prospectively recorded in the hospital's administrative system. The retrospective design here, on the other hand, possibly gives these parameters a more accurate value, as the surgeons are not biased by the knowledge that their surgical outcomes are to be measured. However, outcomes such as intraoperative and postoperative complications, as well as Charlson comorbidity score, may suffer from underreporting. To compensate for this, medical files at the different departments in the hospital (Gynecology, Oncology, Surgery and Internal Medicine, as well as Anesthesia) were scrutinized, to catch possible complications that the patients sought care for. This bias should be comparable between the groups and hence constitutes a non-differential misclassification. Possibly there could be a systematic error due to the fact that registration of adverse events has been more carefully done in recent years than in the past, and therefore underreporting may have been more frequent in the open surgery group. In addition, complications treated at other health care settings could have been missed. On the other hand, emergency care in Sweden is all public, with no private hospitals offering emergency care.

Consequently, all severe complications are likely to be registered. To systematically classify postoperative complications, the widely used CD classification system was applied.[95] Possibly the panorama of postoperative complications would have been even more sophisticatedly described if the Comprehensive Complication Index had been used.[134] This index originates from the CD classification system, but takes into account possible multiple complications. The score is 0–100, and summarizes the overall burden of postoperative complications for the patient.

Lymph node status and tumor characteristics are well documented in the original pathologist's review report and are therefore considered to be valid data. Histopathology assessments are known to suffer from inter- and intraindividual discrepancies, including lymph node counts, which probably applies even to this material. All materials on included patients have been by reviewed by an expert pathologist specialized in gynecological tumors, increasing the likelihood of a uniform assessment. Information on recurrences and adjuvant treatment was collected from the medical records instead of registers, to ensure as complete a coverage as possible on these parameters. Every patient is continuously followed at the outpatient clinic and information on recurrences and treatments given is systematically recorded. Hence, these parameters are considered reliable.

The data on survival relies on the SQRGC and Swedish Population Register, both using the unique Swedish identification number allocated to all inhabitants. Data on vital status is updated daily and hence provides accurate information on the day data was collected.

Analyses on health care costs are based on the national case costing system, CPP, which was chosen because it takes into account actual costs for specific health care contacts, such as a surgical procedure or an admission, for the specific patient, and is not based on an estimated standard cost. Other methods for calculating costs are available, but in the Swedish setting, CPP is considered a reliable and feasible option. Analyses of different methods for the intricate task of calculating health care costs go beyond the scope of this thesis. In Paper I, costs were calculated based on the price per minute in the operating theater and per day at the hospital where patients were treated. This has resulted in lower costs per unit for patients treated with open surgery, since this was done at the local hospitals in the region, compared to the overall higher costs for health care at the tertiary center, SUH. These analyses give an idea of the health care costs for patients treated in that era, with robotic surgery exclusively available at SUH, but not necessarily an accurate comparison of the two modalities, were they used at the same center, and may hence compromise external validity. But again, using the CPP system we aimed to calculate the actual costs, in contrast to using estimations. In Paper II, two patients defined as outliers in the robotic group were excluded from the calculations. They both represented extreme costs, due to prolonged care in the ICU, attributed to anesthetic complications arising at induction of anesthesia. Whether to include them in the calculations or not is a matter of choice, and will obviously have implications on the overall mean costs. We chose to exclude them from our published results, based on the rationale that they were not "robot-specific" costs. The mean basic cost for the robotic group was 13 036 USD when these two outliers are added, compared to 11 921 USD when they were excluded.

A potential source of differential misclassification is the fact that the two persons responsible for collecting the data from the medical records and administrative systems were not blinded to which surgical modality had been used. This is known to constitute a risk of more favorable outcomes in the modality the person believes in. We aimed to overcome this risk through standardized categories for all outcomes, but it is a potential bias that we cannot evaluate.

In Paper IV, clinically significant difference, often referred to as Minimal important difference (MID) was specified for the used questionnaires. For EORTC QLQ-C30, definitions for each subscale were defined in a publication summarizing literature and experts' opinion, were the MID takes into account whether it reflects a deterioration or improvement.[102] No similar comprehensive definition is available for EN24. In publications where MID is defined, it is often set to +/-5 points, which we have used as well. For GAD-7 and PHQ-9, a clinically relevant difference is often set to 5 points, but the cut point ≥10 is often used as the relevant measure to identify patients with clinical symptoms. The heterogenicity of MIDs in the literature hampers comparisons between studies, but greater of a problem is the obvious lack of defined MIDs in publications, were 'changes' in HRQoL is reported based on statistically significant differences. It can also be discussed if added valuable information would have been gain if other instruments, i.e., generic instruments for HRQoL, would have been used. For PROs there is the potential of patients not answering according to the truth, but rather what they believe is expected from them. This may have interfered with our results in different directions.

### 5.1.3 Confounders

When analyzing associations between exposures and outcomes, there is a risk of mixing the effects of the exposure with the effects of other variables. These variables are known as confounders. In observational studies, there is always a risk of confounding, which may to some extent be controlled for in statistical models. Nevertheless, there will be other covariates, that may or may not influence the outcomes. Some of these can be identified, but some will remain unknown. For confounding to occur, a variable must be associated with the studied exposure and causally related to the outcome, and should not be part of the causal chain between the two.

In all four papers, several but few surgeons took part. For all surgical modalities, the individual surgeon's proficiency is of importance, and this may have an impact on outcomes that we cannot measure or control. To prevent this confounding parameter to some extent, in Papers II and III we only included patients operated by at least one subspecialist in gynecologic oncologic surgery.

Comparing a historical cohort with a more recent cohort may have an impact on crucial outcomes such as survival and DFS, but also outcomes such as length of hospital stay and costs could be influenced by this time trend bias. For example, the quality of CPP calculations improves with time. Other factors that could affect outcomes in a positive direction in the later period are increased attention to smoking cessation, early mobilization, a trend towards shorter admissions, and other preventions of postoperative complications. The OS in the general population is increasing with time, seen as an increased life expectancy of one year for women in Sweden during the study period of Paper II and III.[135] Reasons for this are multifactorial including focus on healthy living and improved socioeconomic status, and likely affect the EC population as well. But possibly other factors associated with progress over time, that we are not aware of, constitute risks of confounding, which should be considered when interpreting these results.

Cox proportional hazard model, which we used, enables testing of any difference in survival between particular groups while allowing for other factors; hence, it is a multiple regression model. In Cox's regression model, it is assumed that the hazard of dying/being diagnosed with a recurrence, is proportionate over time. The factors chosen for the Cox regression model in Paper III (surgical method, age, FIGO stage, histologic risk group) are known to impact long-term outcomes in the general EC population and could be related to the studied exposure, surgical modality. Our sample sizes were limited and the outcomes death and recurrence are rare in a diagnosis associated with a fairly good prognosis, such as EC, limiting the possibilities for sophisticated analyses. One possibility may be taking the comorbidity score and/or ASA score into the regression analysis since this would theoretically have an impact on OS and be associated with the selected surgical modality in the later robotic group, and hence be unbalanced between the groups.

In Paper IV, the heterogenicity of the included patients constitutes a potential bias and may affect how we interpret patients HRQoL after receiving EC diagnosis and undergoing robotic surgery. If our sample size were larger it would have been interesting to present stratified results, possibly based on patients' preoperative mental health status, age or adjuvant therapy.

### 5.1.4 Random errors and sample size

No matter how well designed a study may be, the variability in data due to chance will still be there to cause random errors. Both systematic and random errors can skew results. Random errors are minimized by increasing the sample size. In the present studies, we have limited sample sizes, which is commonly seen in studies evaluating surgery for specific diagnoses, not depending on register data. As a result, we found some broad CIs and possibly missing the opportunity to reject the null hypothesis with a high p-value, due to lack of power. Power analysis was done for Paper II and III, regarding postoperative complications. This was chosen based on early publications on robotic surgery reporting complication rates, and effect sizes could be questioned. Ideally, further power calculations should have been done, to know for which outcomes we could expect sufficient power. With the study design chosen, we were restricted in possibilities to increase the power with the expected discrete effect sizes for these outcomes. The risk of type II errors must hence be taken into consideration when evaluating our results, and in future studies, power considerations should be prioritized.

### 5.1.5 External validity

External validity implies whether findings can be generalized to other populations, beyond the one studied. The fact that our results are mainly based on single center studies may reduce external validity. The single center approach may on the other hand reduce confounding that can arise when multiple centers are including patients, and therefore increasing internal validity, which is also a foundation for external validity. The composition of a population and the factors associated with transition in time may impair reproducibility. Taken together there are threats to the external validity of our findings throughout the papers. However, public university hospital settings in other regions/countries in the western world, could offer a similar situation and hence results be generalized.

## 5.2 General discussion

New surgical techniques are usually implemented in clinical practice without preceding safety studies and their impact will, as surgery in general, be affected by the patients' characteristics and surgeons' proficiency. Robotic surgery in gynecological cancer has gained an enormous spread and appreciation, without adequate studies proving its superiority over other modalities. Treatment of EC has in many settings undergone a paradigm shift from open surgery to the new laparoscopic robotic technique. Being the most common gynecological malignancy, this transition impacts many women, as well as impacting the health care systems treating EC.

The aim of this thesis was to investigate short and long-term outcomes of robotic surgery for EC. A special focus has been addressed to the challenging groups of elderly and obese patients, who constitute a large proportion of women with EC. In addition to the objective surgical outcomes and survival, we have paid attention to the increasingly recognized HRQoL and cost effectiveness, essential for the introduction of new techniques. Many observational studies, often on historical cohorts, are available comparing robotic surgery and other modalities. As mentioned, RCTs on robotic surgery for EC are few and lack long-term results.

*Complications*

Keeping complications to a minimum has several benefits, and is of uttermost importance in frail patients, where a complication can have critical consequences. Our results show that the rate of postoperative complications in elderly and obese patients seems to be lower after robotic surgery, compared to open surgery.

This is in line with the overall perception in the literature, which mainly reports on the general EC population. For most patients, a postoperative complication CD grade I–II will pass without severe discomfort or sequelae, but it may have serious medical effects among elderly and obese patients. A surgical modality resulting in reduced complication rates will in addition have the possibility to be cost effective in the long run. A few observational studies on obese patients undergoing robotic surgery are available today, and they present findings similar to ours regarding postoperative complications.[112, 115] The rates vary depending on how complications have been classified, but the tendency towards fewer complications after robotic surgery is clear. Open surgery has been shown to be associated with increased risk of postoperative complications in patients ≥60 years old, while younger patients did not display the same increase.[113] The advantage of MIS is hence greater in the elderly, and the technique may prevent possible severe complications including ileus, pneumonia, and cardiac events in this patient group. Elderly patients (>85 years) are more prone to perioperative mortality when undergoing surgery for EC, which possibly correlates with the increased risk of complications.[136] Accordingly, the importance of minimizing complications perioperatively in this patient group should be emphasized and should be central to the planning and performance of their care. Thanks to the SLN technique being practiced in many settings now, we may see a reduction in complications, while simultaneously allowing elderly patients adequate staging, without jeopardizing the safety of these vulnerable women. It is possible that reduced complications in addition have a positive impact on HRQoL and effects in relation to this.

Chronological age and BMI are measured and set the scene for perioperative risk assessment in many cases. Probably, a greater focus should be on biological age, performance status, and comorbidities when trying to evaluate a patient's capacity to tolerate surgery.

*Costs*

Many early publications on costs were from the US, and these costs are not necessarily representative of the Swedish (or even European) setting. In Sweden, practically all health care, and specifically cancer care, is public. This reduces the different health care panoramas seen in some countries with extensive private (profit-based) settings and private insurances, and treatments adapted to that reality. Accordingly, the Swedish EC cohort is unselected in that aspect, increasing validity. Therefore, results on absolute costs may be inappropriate to compare with results from settings where public health is not the mainstay.

Results in this thesis were not able to show a difference in costs between the two modalities, including analyses of the selected elderly cohort. Taking into account the existing literature on costs for robotic surgery for EC, no conclusion can be drawn on these costs in general, although more recent reports indicate the technique to be less expensive than open surgery. Cost effectiveness has, however, been shown to increase with centralized care that results in a high utilization of the robotic systems and proficient surgeons. A Swedish study from 2013 illustrated that operative time and length of hospital stay are two adjustable main cost drivers which finding is applicable to our material.[98] Their analysis was, however, based on radical hysterectomy for cervical cancer, which, being a more advanced surgical procedure, may have affected costs differently than surgery for EC. The robotic system at SUH has a high utilization, with about 400 cases (gynecologic and urologic) yearly. Throughout the findings in the present papers, operative time was shorter for robotic surgery or equal to that of open surgery; and length of stay was constantly significantly shorter for robotic surgery. This is probably the main reason for equal costs between the two modalities, since robotic surgery is accompanied by additional upfront investment and maintenance costs as well as disposable materials.

Few studies on cost analyses meet suggested criteria for cost calculation.[137] Although this is hard to achieve, future high-quality studies would be needed to reach consensus. Possibly a cost-effectiveness analysis should be made, taking into account the relative costs and the outcome for the intervention studied. In such a model, a difference between the exposures studied need to be shown and added into the calculations.

How the individual hospitals utilize their robotic system will always influence the costs and should, hence, be in focus, perhaps rather than calculation of actual krona and dollars, when aiming at cost analysis and at making the care cost effective. Today’s situation with only one manufacturer of robotic surgical systems, influences costs and may be attributable to change in the future. Together, the evidence at hand suggests that the earlier perception regarding costs for robotic surgery needs to be reevaluated, and that the economic argument for not offering robotic surgery to patients who may benefit from the technique needs to be abandoned.

*Survival*

Long-term survival after robotic surgery for EC has been considered equal to open surgery based mainly on two large RCTs on survival and recurrence after conventional laparoscopy.[34, 35] Observational studies comparing robotic surgery to open surgery have shown a similar trend, but without convincing conclusions.[52, 53] There are, to our knowledge, no RCTs evaluating long-term survival and recurrence after robotic surgery. Neither is long-term survival in frail groups of elderly and obese patients well reported.

Results in the present thesis indicate an equivalent long-term prognosis for robotic and open surgery in obese and elderly patients with EC. This is reassuring for these, often frail patients, being at increased risk of diagnosis and possibly being the greatest beneficiaries of the robotic technique in short-term outcomes.

Potential causes resulting in inferior survival after MIS in general, and robotic surgery in particular, have been debated extensively but are mainly theoretical speculations. The inferior oncological outcomes for patients with early-stage cervical cancer presented in the LACC trial, and others, have caused extensive discussion.[55, 138, 139] Earlier ideas based on preclinical studies, of an irritation of the peritoneal environment caused by the introduction of pneumoperitoneum, with subsequent accidental presentation of tumor cells to the circulating CO2, provoking cancerous cell implantation, have revived.[140, 141] In addition, there has been suggestions that the use of a uterine manipulator and intracorporeal colpotomy may shred tumor fragments to the pelvis, and hence risk of recurrences.[55, 142] Some of these theories could be translated to MIS in EC. Considering the origin and growth pattern of the two malignancies these potential risks should be less prominent in EC, particularly in stage 1A and B. Invasive uterine manipulators are not recommended or used in gynecologic oncology in Sweden. Up until today, there is, however, no evidence to question the generalization of results from RCTs on conventional laparoscopy for EC to robotic surgery, and the robotic technique may be considered safe for elderly and obese patients with EC.

*Elderly*

Elderly persons have fewer physiological reserves in a situation of stress caused by surgery or complications perioperatively. This may not only result in higher rates of complications, but complications also potentially become more lethal. Whether age is an independent risk factor for postoperative complications is not obvious. Age >85 has, however, been shown to be associated with increased risk of non-surgical postoperative complications.[136] Complications prone to elderly in addition include a palette of complications not seen in other ages, e.g., falls and confusion.[91] New oncogeriatric scores are being developed to improve detection of patients at increased risk of complications, and optimize their care accordingly.[91]

In has been suggested that the increased operative time often reported for MIS may constitute a risk to elderly. This has been studied in colorectal surgery and not proven true.[143] The reduced length of hospital stay after MIS probably counteracts this risk. At our institution, with experienced gynecologic oncology surgeons performing all procedures, the operative time was no longer for robotic surgery than for open surgery in the elderly, and this potential risk is not a reality in settings like ours. There is no general consensus on the definition of "elderly," in terms of risks following surgery and the age limits set differ between studies. Chronological age is probably a non-specific measure to identify those at most risk; instead, an adequate frailty score is desirable. Different scores have been suggested, but often the ones that have the better predictability are too time-consuming to be clinically useful and research needs to identify the most prognostic factors for frailty.

*Obese women*

Women with increased weight classified as overweight or obesity offer a challenge to themselves and to health care professionals caring for them. These patients are at increased risk of several diagnoses, EC included, due to their habitus; and simultaneously treatments offered pose increased risk of complications due to these patients' weight and accompanying comorbidities. An increased number of comorbidities increases the risk of complications; also, it has been shown that overweight is associated with increased risk of lower HRQoL.[56, 144] In 2008, results of a relatively small cohort study of obese and morbidly obese (≥40 kg/m$^2$) patients emphasized the feasibility of MIS in treating EC in this patient group, when presenting robotic surgery as a valid and possibly generalizable modality.[145] Since then, several observational studies on obese patients undergoing robotic surgery have been published. In MIS, including robotic surgery, obesity is associated with higher risks of conversion to open surgery and for this reason, the feasibility of the technique is questioned by some.[146] Nevertheless, the robotic technique has been proposed as method of choice in obese patients, due to advantages seen. Still, long-term follow-ups are needed to safely support this conclusion.[147]

An obese patient in need of surgery for a life-threatening condition is believed to be at increased risk during all parts of the procedure. Challenges range from difficulties in performing an ideal preoperative work-up and induction of anesthesia, through the obvious obstacles of good access and vision during the surgical procedure to avoid intraoperative complications to simultaneously maintaining a positive airway pressure and adequate oxygenation. Thereafter, direct postoperative problems can follow, with immobilization and effects of these, wound complications and later postoperative complications, and, ultimately, perioperative mortality. Some aspects do not actually have clear evidence in the literature, possibly due to the fact that obese patients are not included in studies to the same extent as others. Nevertheless, this patient group should obviously be entitled to the same standards of care, without jeopardizing their safety.

For successful robotic surgery, a well-functioning team in the operating room is of importance, and in fragile cases, such as obesity and elderly, this is crucial. The preoperative work-up should integrate both anesthetic and surgical concerns and be optimized for the individual patient. Pre- and intraoperative measures should be performed and continuous communication within the team throughout the procedure is critical. These factors are likely to develop over time and consolidate once a technique is implemented.

In Paper III, we present a homogenous cohort of obese patients undergoing surgery for EC with two different modalities. The results show that this procedure is feasible with either modality in obese patients. The intra- and postoperative complications were generally low and survival comparable to the general EC population. However, robotic surgery appears to be advantageous for obese patients in terms of a reduction in EBL, shorter hospital stay, and fewer postoperative complications, which are all considered beneficial, especially in this patient group.

Studies on long-term survival and recurrence rates in obese patients are lacking in the literature. Despite the drawback of a retrospective observational design, our study on this homogenous obese cohort still offers a unique presentation of long-term outcomes, indicating that robotic surgery is safe in all respects.

*Health-related quality of life*

Health-related QoL data is needed in health care generally, and particular interest has lately been shown in cancer patients' HRQoL. Patients' experiences of care are central in evaluating efficacy of treatments given, and PROs allow us access to information we cannot grasp through other measures. From the results in this thesis, we summarize that undergoing robotic surgery for EC seems to have a transient but mild negative impact on women's HRQoL. The decrease in GHS together with physical and role functioning, seen 2 weeks after surgery, is not surprising, and scores returned to baseline levels at 3 months, as has been shown in previous studies and our results confirm this conclusion.[123-125, 127]

There was an increase in anxiety symptoms among our study population after receiving the cancer diagnosis and while awaiting treatment. It is promising that these symptoms decreased already 2 weeks postoperatively, when many of the women had not yet received information about their final pathology report or started adjuvant therapy. This promising finding is further emphasized by the increase in emotional and cognitive functioning seen at 3 months postoperatively. It may be speculated that the diagnosis itself, in addition to undergoing surgery, is associated with fear and anxiety in many patients. The fact that patients' habitual HRQoL scores and symptoms of anxiety and depression are not known, prevents us from drawing conclusions about the sequence of events. One should also bear in mind, that psychological well-being, is associated with several other factors, like social vulnerability, possibly impacting HRQoL. Other ideas, supported by increased levels of HRQoL after completed surgery in some studies, suggest that suffering from cancer and receiving treatment aiming at cure may change patients' expectations on life and, hence, their ability to cope with symptoms and other issues in general, which may affect domains of life quality in a positive way.

Health-related QoL after conventional laparoscopy and open surgery for EC has been compared in two RCTs reporting greater improvement in HRQoL up to 6 months after laparoscopy.[148, 149] More recently, two Swedish RCTs have compared robotic and open surgery regarding its effects on HRQoL: Lundin et al. reported a faster recovery in HRQoL during the first 6 weeks for women undergoing robotic surgery, but the clinical significance can be questioned.[127] Salehi et al. evaluated HRQoL 1 year after surgery and found no difference between the methods.[150]

It may be concluded that further studies are needed to adequately evaluate HRQoL in EC and its various treatments including primary surgery. Knowledge about patients' experiences of the peri- and postoperative course should be used in the preoperative information to the patients and to provide guidance in the postoperative period.

# 6. Conclusion

The results in this thesis investigating primary surgery in EC indicate that:

- Robotic surgery is associated with significantly reduced EBL and length of hospital stay compared to open surgery, also in obese and elderly women.

- Robotic surgery in obese women is associated with fewer postoperative complications compared to open surgery.

- Long-term survival and recurrence rates seem to be equal for robotic and open surgery.

- Health care costs, seem not to be increased, even in elderly patients, by the use of robotic compared to open surgery, in a setting with a well-utilized robotic system.

- Health-related QoL is reduced in the immediate postoperative period after robotic surgery, but returns to baseline levels within 3 months.

- Receiving diagnosis and undergoing treatment with robotic surgery seems not to increase the number of women with clinically significant symptoms of anxiety or depression, 3 months postoperatively.

Taken together, robotic surgery should be the recommended surgical modality in treating women with EC, including obese and elderly women.

# 7. Future perspectives

Robotic surgery has developed rapidly since its introduction and the technique is here to stay. Further evolution of the technique is to be expected, and scientific work needs to continue to secure and evolve how robotic surgery is used safely in gynecologic cancers including EC and to determine whom to offer the technique in situations where robotic access may be limited.

To have reliable evidence of robotic surgery and its effect on long-term oncological outcomes, including recurrence rates, further studies are warranted. With the generally favorable prognosis and few events in EC, this may be done through well-designed large population-based observational studies, although offering challenges. Analyses stratified by age and BMI-groups would be desirable, to specifically evaluate results in these risk-groups.

Studies comparing surgical modalities will always be biased by the individual surgeon's proficiency and experience, and possibly research should aim to try to standardize surgical procedures in an attempt to minimize the potential effect of an individual surgeon.

With an increased implementation of the SLN technique, most women will probably be offered adequate staging and risk assessments based on surgical stage and histopathology. In order to increase survival and decrease treatment side effects, however, a valid algorithm to guide the decision on whom to offer adjuvant therapy is desirable. With today's increasing knowledge about molecular subgroups within EC, there is a potential of a breakthrough in the area risk assessment and medical oncology for EC. Future studies can possibly utilize this more specific molecular and genetic information about EC to develop treatment guidelines including surgery tailored to the individual woman's tumor.

High age and obesity are challenging factors in health care in general and in surgery in particular. It is important for research to cover complete patient populations, including obese and elderly patients. However, based on current evidence chronological age and BMI levels alone seem to be insufficient to evaluate risks and tailor treatments. Research should aim to develop a valid frailty score to accurately assess women and their risks during and after surgery. Other patient characteristics, influencing oncological outcomes, including socioeconomic factors, should be taken into consideration. Such a frailty score is needed also for women with other gynecological malignancy, and could hence be used broadly.

Costs for health care in general and new techniques in particular will always need to be taken into consideration. The total economic burden of robotic surgery is not clear, but with increased experience and competition among manufacturers, the additional costs should become less and future studies related to costs should aim to develop well utilized, cost efficient robotic system, making the care cost effective and increase availability.

Health-related QoL after treatment for EC is still underexplored. Further longitudinal follow-ups in larger cohorts of EC survivors should be carried out, including analyses to identify women at higher risk of impaired HRQoL, and ideally protective factors. It would be of interest to follow population-based cohorts, possibly nationwide, over several years, including socioeconomic variables, to identify subgroups of patients in need of special attention. Today's knowledge of patients' experiences of undergoing treatment for EC should be used in a systematic way to guide patients through their peri- and postoperative phase.

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# EORTC QLQ-C30 (version 3)

Vi är intresserade av några saker som har med dig och din hälsa att göra. Besvara alla frågor genom att sätta en ring runt den siffra som stämmer bäst in på dig. Det finns inga svar som är "rätt" eller "fel". Den information du lämnar kommer att hållas strikt konfidentiell.

Fyll i Dina initialer: |_|_|_|_|
När är Du född? (Dag, Månad, År): |_|_|_|_|_|_|_|_|
Dagens datum (Dag, Månad, År): 31 |_|_|_|_|_|_|_|_|

---

| | | Inte alls | Lite | En hel del | Mycket |
|---|---|---|---|---|---|
| 1. | Har du svårt att göra ansträngande saker, som att bära en tung kasse eller väska? | 1 | 2 | 3 | 4 |
| 2. | Har du svårt att ta en <u>lång</u> promenad? | 1 | 2 | 3 | 4 |
| 3. | Har du svårt att ta en <u>kort</u> promenad utomhus? | 1 | 2 | 3 | 4 |
| 4. | Måste du sitta eller ligga på dagarna? | 1 | 2 | 3 | 4 |
| 5. | Behöver du hjälp med att äta, klä dig, tvätta dig eller gå på toaletten? | 1 | 2 | 3 | 4 |

## Under veckan som gått:

| | | Inte alls | Lite | En hel del | Mycket |
|---|---|---|---|---|---|
| 6. | Har du varit begränsad i dina möjligheter att utföra antingen ditt förvärvsarbete eller andra dagliga aktiviteter? | 1 | 2 | 3 | 4 |
| 7. | Har du varit begränsad i dina möjligheter att utöva dina hobbyer eller andra fritidssysselsättningar? | 1 | 2 | 3 | 4 |
| 8. | Har du blivit andfådd? | 1 | 2 | 3 | 4 |
| 9. | Har du haft ont? | 1 | 2 | 3 | 4 |
| 10. | Har du behövt vila? | 1 | 2 | 3 | 4 |
| 11. | Har du haft svårt att sova? | 1 | 2 | 3 | 4 |
| 12. | Har du känt dig svag? | 1 | 2 | 3 | 4 |
| 13. | Har du haft dålig aptit? | 1 | 2 | 3 | 4 |
| 14. | Har du känt dig illamående? | 1 | 2 | 3 | 4 |
| 15. | Har du kräkts? | 1 | 2 | 3 | 4 |
| 16. | Har du varit förstoppad? | 1 | 2 | 3 | 4 |

Fortsätt på nästa sida

## Under veckan som gått:

| | | Inte alls | Lite | En hel del | Mycket |
|---|---|---|---|---|---|
| 17. | Har du haft diarré? | 1 | 2 | 3 | 4 |
| 18. | Har du varit trött? | 1 | 2 | 3 | 4 |
| 19. | Har dina dagliga aktiviteter påverkats av smärta? | 1 | 2 | 3 | 4 |
| 20. | Har du haft svårt att koncentrera dig, t.ex. läsa tidningen eller se på TV? | 1 | 2 | 3 | 4 |
| 21. | Har du känt dig spänd? | 1 | 2 | 3 | 4 |
| 22. | Har du oroat dig? | 1 | 2 | 3 | 4 |
| 23. | Har du känt dig irriterad? | 1 | 2 | 3 | 4 |
| 24. | Har du känt dig nedstämd? | 1 | 2 | 3 | 4 |
| 25. | Har du haft svårt att komma ihåg saker? | 1 | 2 | 3 | 4 |
| 26. | Har ditt fysiska tillstånd eller den medicinska behandlingen stört ditt familjeliv? | 1 | 2 | 3 | 4 |
| 27. | Har ditt fysiska tillstånd eller den medicinska behandlingen stört dina sociala aktiviteter? | 1 | 2 | 3 | 4 |
| 28. | Har ditt fysiska tillstånd eller den medicinska behandlingen gjort att du fått ekonomiska svårigheter? | 1 | 2 | 3 | 4 |

## Sätt en ring runt den siffra mellan 1 och 7 som stämmer bäst in på dig för följande frågor:

29. Hur skulle du vilja beskriva din hälsa totalt sett under den vecka som gått?

1 2 3 4 5 6 7

Mycket dålig Utmärkt

30. Hur skulle du vilja beskriva din totala livskvalitet under den vecka som gått?

1 2 3 4 5 6 7

Mycket dålig Utmärkt

# EORTC QLQ – EN24

Patienter berättar ibland att de har följande symtom eller besvär. Markera i vilken utsträckning som du har upplevt dessa symtom eller besvär genom att ringa in den siffra som passar bäst in på dig.

| | **Under veckan som gått:** | **Inte alls** | **Lite** | **En hel del** | **Mycket** |
|---|---|---|---|---|---|
| 31. | Har du haft bensvullnad/svullna ben? | 1 | 2 | 3 | 4 |
| 32. | Har du haft tyngdkänsla i ena eller båda benen? | 1 | 2 | 3 | 4 |
| 33. | Har du haft ont i nedre delen av ryggen och/eller bäckenet? | 1 | 2 | 3 | 4 |
| 34. | När du kände att du behövde kissa, var du då tvungen att skynda dig till toaletten? | 1 | 2 | 3 | 4 |
| 35. | Har du kissat ofta? | 1 | 2 | 3 | 4 |
| 36. | Har du haft urinläckage? | 1 | 2 | 3 | 4 |
| 37. | Har du känt smärta eller sveda när du kissar? | 1 | 2 | 3 | 4 |
| 38. | Då du kände att du behövde tömma tarmen, var du då tvungen att skynda dig till toaletten? | 1 | 2 | 3 | 4 |
| 39. | Har du haft avföringsläckage? | 1 | 2 | 3 | 4 |
| 40. | Har du besvärats av gaser/gasavgång? | 1 | 2 | 3 | 4 |
| 41. | Har du haft knipsmärtor i buken? | 1 | 2 | 3 | 4 |
| 42. | Har du känt dig uppblåst i buken? | 1 | 2 | 3 | 4 |
| 43. | Har du haft stickningar eller domningar i händer eller fötter? | 1 | 2 | 3 | 4 |
| 44. | Har du haft värk i muskler eller leder? | 1 | 2 | 3 | 4 |
| 45. | Har du tappat hår? | 1 | 2 | 3 | 4 |
| 46. | Har mat och dryck smakat annorlunda än vanligt? | 1 | 2 | 3 | 4 |

**Fortsätt på nästa sida**

| | **Under veckan som gått:** | **Inte alls** | **Lite** | **En hel del** | **Mycket** |
|---|---|---|---|---|---|
| 47. | Har du känt dig mindre attraktiv till följd av sjukdomen eller behandlingen? | 1 | 2 | 3 | 4 |
| 48. | Har du känt dig mindre kvinnlig till följd av sjukdomen eller behandlingen? | 1 | 2 | 3 | 4 |

| | **Under de senaste fyra veckorna:** | **Inte alls** | **Lite** | **En hel del** | **Mycket** |
|---|---|---|---|---|---|
| 49. | I vilken utsträckning var du intresserad av sex? | 1 | 2 | 3 | 4 |
| 50. | I vilken utsträckning var du sexuellt aktiv? | 1 | 2 | 3 | 4 |
| | **Besvara följande frågor endast om du varit sexuellt aktiv under de senaste 4 veckorna:** | 1 | 2 | 3 | 4 |
| 51. | Har slidan känts torr vid samlag/sex? | 1 | 2 | 3 | 4 |
| 52. | Har slidan känts kort/trång? | 1 | 2 | 3 | 4 |
| 53. | Har du haft smärta vid samlag/sex? | 1 | 2 | 3 | 4 |
| 54. | Var sex till glädje för dig? | 1 | 2 | 3 | 4 |

Kod:________

# PHQ-9

Under de senaste 2 veckorna, hur ofta har du besvärats av något av följande problem.

| | Inte alls | Flera dagar | Mer än hälften av dagarna | Nästan varje dag |
|---|---|---|---|---|
| 1. Lite intresse eller glädje i att göra saker | 0 | 1 | 2 | 3 |
| 2. Känt dig nedstämd, deprimerad eller känt att framtiden ser hopplös ut. | 0 | 1 | 2 | 3 |
| 3. Problem att somna eller att du vaknat i förtid, eller sovit för mycket | 0 | 1 | 2 | 3 |
| 4. Känt dig trött eller energilös | 0 | 1 | 2 | 3 |
| 5. Dålig aptit eller att du ätit för mycket | 0 | 1 | 2 | 3 |
| 6. Dålig självkänsla - eller att du känt dig miss- lyckad eller att du svikit dig själv eller din familj | 0 | 1 | 2 | 3 |
| 7. Svårigheter att koncentrera dig, till exempel när du läst tidningen eller sett på TV | 0 | 1 | 2 | 3 |
| 8. Att du rört dig eller talat så långsamt att andra noterat det? Eller motsatsen – att du varit så nervös eller rastlös att du rört dig mer än vanligt | 0 | 1 | 2 | 3 |
| 9. Tankar att det skulle vara bättre om du var död eller att du skulle skada dig på något sätt | 0 | 1 | 2 | 3 |

10. Om du kryssat för att du haft något av dessa problem, hur stora svårigheter har dessa problem förorsakat dig på arbetet, eller för att ta hand om sysslor hemma, eller i kontakten med andra människor?

| Inga svårigheter | Vissa svårigheter | Stora svårigheter | Extrema svårigheter |
|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ |



VÄND ↷

Kod:______

# GAD-7

Under de senaste 2 veckorna, hur ofta har du besvärats av något av följande problem.

| | Inte alls | Flera dagar | Flertalet dagar | Så gott som dagligen |
|---|---|---|---|---|
| 1. Känt mig nervös, orolig, spänd | 0 | 1 | 2 | 3 |
| 2. Inte kunnat låta bli att ängslas | 0 | 1 | 2 | 3 |
| 3. Ängslats för mycket för olika saker | 0 | 1 | 2 | 3 |
| 4. Haft svårt att koppla av | 0 | 1 | 2 | 3 |
| 5. Varit så rastlös att det varit svårt att sitta still | 0 | 1 | 2 | 3 |
| 6. Varit retlig och lättstörd | 0 | 1 | 2 | 3 |
| 7. Varit rädd, som om något förfärligt skulle kunna hända | 0 | 1 | 2 | 3 |

Om något av detta förekommit, hur påverkade det din arbetsförmåga, hemsysslor ochrelationer?

Inte alls ☐
Lite ☐
Mycket ☐
Påtagligt störande ☐

Översättning av Christer Allgulander Ref Spitzer et al. Arch Intern Med 2006;166:1092-97

VÄND ↷