Endometrial Cancer

Studies on recurrences, complications and preoperative diagnostics

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Abstract

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Introduction: The most common gynecological cancer is Endometrial Cancer (EC). The prognosis is generally favorable, mainly due to an early diagnosis. However, there are subgroups of EC with a higher risk for metastases and recurrences resulting in poorer survival. Primary treatment for EC is surgical, with hysterectomy and bilateral salpingo-oophorectomy and in higher risk groups adding surgical staging with lymph node assessment for the adjuvant treatment planning.
Aim: The overall aim of this thesis was to study recurrence, survival and surgical complications in a population-based cohort and to assess the introduction of the first national guidelines (NGEC), which recommended pelvic and para-aortic lymphadenectomy (PPLND) in high-risk EC. A second aim was to evaluate preoperative risk classification assessment with transvaginal ultrasound (TVUS) and magnetic resonance imaging (MRI) in low-grade endometrioid EC.
Methods: Paper I-III were regional population-based studies in the Western Sweden Health Care Region (WSHCR). Data was retrieved from the Swedish Quality Register for Gynecological Cancer (SQRGC) for all EC patients in the WSHCR 2010-2017. Medical records were reviewed for details of recurrence, complications, and patient characteristics, such as BMI and comorbidities. Patients with primary surgical treatment for pre-operative early-stage EC were included in the studies. Paper I encompassed patients with endometrioid EC and Paper II non-endometrioid EC. In Paper III, patients who underwent surgery at the tertiary center were included and complications 30 days postoperatively were recorded and graded according to the Clavien-Dindo (CD) classification system. Overall (OS), net (NS) and disease-free survival (DFS) were calculated using the Kaplan-Meier method. The Cox proportional hazards regression model was used in Paper I-III to evaluate the effect of identified variables on DFS and OS. Uni- and multivariable logistic regression analyses were performed with complications as outcome in Paper III.
Paper IV was a prospective multicenter study in the WSHCR including patients with low-grade EC planned for primary surgery during 2017-2019. The patients were examined preoperatively with both TVUS and MRI to assess deep myometrial infiltration (MI) and cervical stroma invasion (CSI) for the decision on surgery with or without PPLND. The TVUS was performed by gynecologists, and the MRI was performed according to a standardized protocol. The methods were analyzed for sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy. The methods were compared using McNemar's test and Cohen's kappa (k).

Results: In the endometrioid EC cohort in Paper I, 8.3% (136/1630) experienced a recurrence. In the non-endometrioid EC cohort in Paper II, the recurrence rate was 29% (67/228). The total 5-year DFS was 83.9% for the endometrioid EC cohort (Paper I) and 61.9% for the non-endometrioid EC cohort (Paper II). If no recurrence occurred, the 5-year OS was 91.9% in the endometrioid EC cohort (Paper I) and 88.5% in the non-endometrioid EC cohort (Paper II). When a recurrence occurred the 5-year OS for the endometrioid EC cohort was 77.0% for isolated vaginal recurrences compared to 36.1% for all other recurrences (Paper I). The 5-year OS was 13.4% when a recurrence occurred in the non-endometrioid EC cohort (Paper II). In Paper I, age, FIGO stage and primary treatment were found independent risk factors for recurrence. In Paper II, the OS before the implementation of NGEC was 57.3% compared to 72.0% after. Age, FIGO stage and lymph node dissection were found significant factors for DFS, where having a lymph node dissection decreased the risk of recurrence or death. In Paper III, 19.7% (108/549) had a surgical complications of CD grade II-V. Surgical technique, BMI and lymph node dissection, were found to be risk factors for complications CD. In Paper IV (n=259), MRI and TVUS were compared for the assessment of deep MI and CSI and there was a statistically significant difference in specificity, with MRI having a higher specificity. No difference in sensitivity was found.
Conclusions: For endometrioid EC, the recurrence rate was overall low in contrast to non-endometrioid EC where the recurrence rate was rather high. The survival was excellent when no recurrence occurred, in both endometrioid and non-endometrioid EC. However, in cases of recurrence, survival was poor, with the exception of isolated vaginal recurrence, where the prognosis was favorable. A significant improvement in survival was seen in non-endometrioid EC after the NGEC implementation with lymph node staging tailoring adjuvant radiotherapy. However, in Paper III we show that surgical staging with lymphadenectomy is a risk factor for surgical complications. This may be taken into consideration in treatment guidelines for EC, where steps moving towards a less extensive lymph node assessment surgery with the sentinel node procedure may be advocated. For the assessment of deep MI, MRI had a higher accuracy than TVUS. Nevertheless, the sensitivity of TVUS performed by gynecologists was evaluated as acceptable and did not differ from MRI. TVUS is readily available, and Paper IV supports this method for first-hand use in similar settings.

Keywords: endometrial cancer, lymphadenectomy, recurrence, survival, surgical complications, diagnostic accuracy

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Sammanfattning på svenska

Livmodercancer, också kallad livmoderkroppscancer, utgår ifrån livmoderns slemhinna. Livmodercancer är den vanligaste gynekologiska cancerformen och drabbar nästan 1500 kvinnor i Sverige per år. Prognosen är överlag god med en femårsöverlevnad på 84% i Sverige. För många är det tillräckligt med en operation med borttagande av livmoder och äggstockar som behandling. Det finns dock typer som har högre risk för spridning, i första hand till lymfknutor. En större operation med borttagande av lymfknutor, så kallad lymfkörtelutrymning, kan då utföras för stadieindelning till hjälp för planering av efterbehandling med cellgift och/eller strålning. Det rekommenderas enligt många internationella riktlinjer inklusive det första nationella vårdprogram som infördes i Västra sjukvårdsregionen 2013. Innan det nationella vårdprogrammet infördes fanns regionala riktlinjer där alla med livmodercancer med hög risk fick efterbehandling med cellgifter och strålning utan borttagande av lymfknutor.

Syftet med denna avhandling var att studera återfall och överlevnad samt kirurgiska komplikationer vid livmodercancer och i synnerhet i samband med införandet av det första nationella vårdprogram som innebar en utökad operation med lymfkörtelutrymning för högriskgruppen. Ett ytterligare syfte var att studera preoperativ riskbedömning med ultraljud utfört av gynekolog jämfört med magnetkameraundersökning. Studierna är utförda i Västra Sjukvårdsregionen som består av Västra Götalands-regionen och norra Halland. Det svenska kvalitetsregistret för gynekologisk cancer (SQRGC) användes för datauttag till delarbete I-III. Registreringen i SQRGC startade 2010 för livmodercancer och Västra sjukvårdsregionen har en mycket hög täckningsgrad mot cancerregistret. Delarbete IV var en prospektiv multicenterstudie.

I delarbete I och II studerades återfall och överlevnad för de patienter som genomgått operation som första behandling under åren 2010–2017. De patienter som ingick i studien hade före operationen bedömts vara i tidigt stadium, dvs de hade ingen uppenbar spridning och var tumörfria när uppföljningen började. I delarbete I ingick 1630 patienter med endometrioid typ, den vanligaste typen. I delarbete II ingick 228 patienter som hade icke-endometrioida typer, som är av mer aggressiv karaktär. Återfallsfrekvensen var lägre hos patienter med endometrioid livmodercancer i delarbete I (8.3%) i jämförelse med icke-endometrioid i delarbete II (29%). Både för

patienter som inte fick återfall och de som fick återfall var överlevnaden bättre för de med endometrioid än icke-endometrioid livmodercancer. De patienter som fick återfall endast i slidan gick det relativt bra för, jämfört om återfallet var någon annanstans eller på flera ställen. Högre ålder, högre tumörstadium och om efterbehandling hade givits var riskfaktorer för återfall för endometrioid livmodercancer. Intressant nog så fann vi i delarbete II, att om lymfknutor hade tagits bort vid operationen så minskade risken för återfall och gav bättre överlevnad, hos patienter med icke-endometrioid livmodercancer. Det var en signifikant förbättrad överlevnad i den senare tidsperioden som förklaras av införandet av det nationella vårdprogrammet med lymfkörtelutrymning för högriskgruppen, inklusive de med icke-endometrioid livmodercancer. Detta trots att de fick efterföljande strål-behandling i betydligt mindre utsträckning.

I delarbete III studerades kirurgiska komplikationer för 549 patienter som hade genomgått operation som första behandling vid Sahlgrenska Universitetssjukhuset under åren 2012–2016. En journalgenomgång genomfördes för att så långt som möjligt upptäcka alla komplikationer upp till 30 dagar efter operationen och de klassificerades enligt svårighetsgrad. Studien visade att komplikationer generellt var ovanliga. Riskfaktorer för komplikationer var övervikt, lymfkörtelutrymning och kirurgisk teknik, där öppen operation gav mer komplikationer än titthålsteknik med robot eller konventionell teknik. Om en kirurgisk komplikation hade inträffat visade det en påverkan på överlevnaden de första 1,5 åren efter operationen men inte senare.

I delarbete IV ingick 259 patienter med låggradig endometrioid livmodercancer som planerades för operation som första behandling under åren 2017–2019. I enlighet med en uppdatering av det nationella vårdprogrammet så skulle den patientgruppen genomgå en preoperativ undersökning av livmodern för bedömning av djupväxt i livmoderns muskelvägg. Vid djupväxt så ökar risken för spridning till lymfknutor och det innebar att operationen förutom borttagande av livmoder och äggstockar även skulle innefatta lymfkörtelutrymning. Vaginal ultraljudsundersökning ingår i en vanlig gynekologisk undersökning, men för bedömningen av djupväxt var bara undersökning av särskilt tränade ultraljudsexperter utvärderad. Syftet med vår studie var att se om ultraljud, genomfört av en gynekolog som handhar livmodercancer-patienter, skulle kunna vara tillräckligt bra. Patienterna genomgick undersökning med både ultraljud och magnetkamera och en jämförelse genomfördes. Resultatet visade att magnetkameraundersökning gav bättre noggrannhet (accuracy), men ultraljudsundersökningen hade inte sämre känslighet (sensitivitet) för att upptäcka djupväxt.

List of Papers

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

I. **Åkesson Å, Adok C and Dahm-Kähler P**
Recurrence and survival in endometrioid endometrial cancer - A populationbased cohort study
Gynecol Oncol. 2023 Jan;168:127-134

II. **Åkesson Å, Adok C and Dahm-Kähler P**
Increased survival in non-endometrioid endometrial cancer after introducing lymphadenectomy and tailoring radiotherapy - A population-based cohort study
Eur J Cancer 2022 Jul;169:54-63

III. **Åkesson Å, Wolmesjö N, Adok C, Milsom I and Dahm-Kähler P**
Lymphadenectomy, obesity and open surgery are associated with surgical complications in endometrial cancer
Eur J Surg Oncol. 2021 Nov;47:2907-2914

IV. **Palmér M*, Åkesson Å*, Marcickiewicz J, Blank E, Hogström L, Torle M, Mateoiu C, Dahm-Kähler P and Leonhardt H**
Accuracy of transvaginal ultrasound versus MRI in the PreOperative Diagnostics of low-grade Endometrial Cancer (PODEC) study: A prospective multicenter study
Clin Radiol. 2023 Jan;78(1):70-79

*=joint first author

Content

Abbreviations

ASA	American Society of Anesthesiologists
BMI	Body Mass Index
BSOE	Bilateral salpingo-oophorectomy
CRF	Case Report Form
CSI	Cervical Stroma Invasion
CT	Computed Tomography
DFS	Disease Free Survival
EBRT	External Beam Radiotherapy
EC	Endometrial Cancer
EIN	Endometrial Intraepithelial Neoplasia
FIGO	International Federation of Gynecology and Obstetrics/ Fédération Internationale de Gynécologie et d'Obstétrique
HR	Hazard Ratio
ICG	Indocyanine Green
INCA	InformationsNätverk för Cancervården
L1CAM	L1 Cell Adhesion Molecule
LVSI	Lymph Vascular Space Invasion
MDT	Multidisciplinary Treatment Board
MI	Myometrial Infiltration
MIS	Minimal invasive surgery
MMR	Mis Match Repair
MMRd	Mis Match Repair deficiency
MRI	Magnetic Resonance Imaging
MSI	Microsatellite instability
NCR	National Cancer Register
NDR	National Death Register
NED	No Evidence of Disease
NGEC	National Guidelines for Endometrial Cancer
NS	Net survival
NSMP	Non-Specific Molecular Profile
OR	Odds Ratio
OS	Overall Survival
P53	Tumor protein p53 or cellular tumor antigen p53
PET-CT	Positron Emission Computed Tomography

POLE	Polymerase-epsilon
PODEC	Pre Operative Diagnostics of low-grade Endometrial Cancer
PPLND	Pelvic and Paraaortic Lymph node dissection/lymphadendectomy
RCT	Randomized Control Trial
RS	Relative Survival
SHR	Sub distribution Hazards Ratio
SQRGC	Swedish Quality Register for Gynecological Cancer
SUH	Sahlgrenska University Hospital
TVUS	Transvaginal Ultrasound/ultrasonography
VBT	Vaginal Brachytherapy
WSHCR	Western Sweden Health Care Region

1. Introduction

Endometrial cancer (EC), originates in the endometrium of the uterus and is the most common type of uterine malignancy. The prognosis is in general favorable with a 5-year relative survival (RS) of 84% in Sweden[1,2]. This thesis is based on four studies exploring recurrence rates and patterns of endometrioid and non-endometrioid EC, surgical complications and preoperative diagnostics in a regional population-based cohort. The clinical setting is the Western Sweden Health Care Region (WSHCR) during the period 2010-2019 and the shifts in treatment guidelines over this time period.

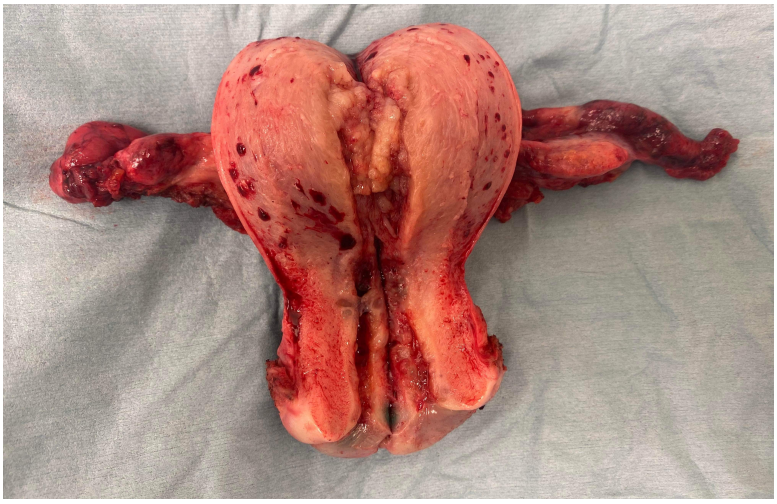

Figure 1. *Hysterectomy specimen with endometrial cancer*

1.1 Epidemiology

The most frequent of the gynecological cancers is EC and almost 1500 women are annually diagnosed with EC in Sweden[2].

Worldwide, EC affects approximately 400000 women per year[3] with pronounced demographic differences where reported incidences range from under 1 to over 40/100000 women. The incidence is highest in North America and some European countries[3,4].

The incidence has been rising since the mid 1900s due to an ageing population and increasing obesity, the main risk factors for EC. Projections have been made for the coming years proposing a continued increase in the US[5]. Looking at the numbers in recent years in Sweden the incidence does not seem to increase, but rather decrease, also in comparison to the neighboring Nordic countries, displayed in the Nordcan data in *Figure 2.* Possible explanations can only be hypothesized but may be partly explained by changes in the population due to migration.

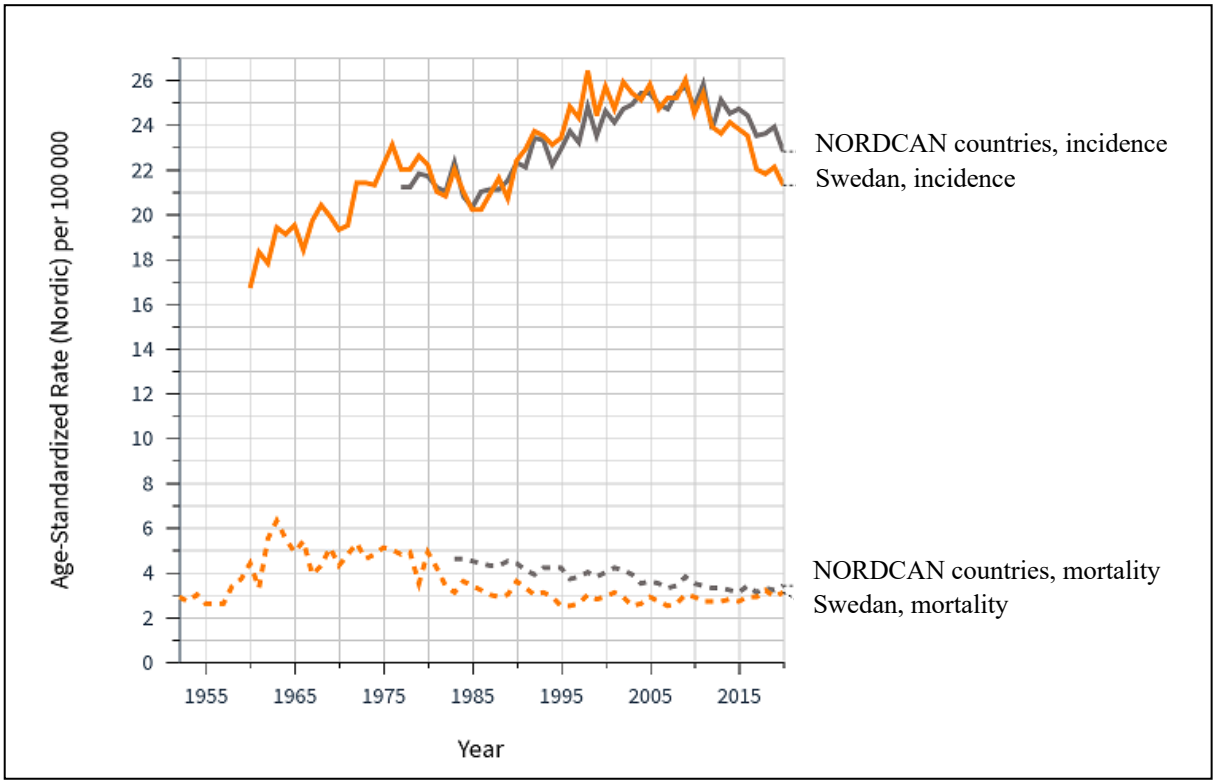

Figure 2. *Endometrial cancer incidence and mortality in Sweden in comparison with the Nordic countries per 100000 females. Nordcan/IARC/WHO[6]*

The peak prevalence for EC occurs around 70 years of age as EC is mostly a disease in the postmenopausal woman. However, about 15% of the women affected are premenopausal and 4% are under 40 years of age[7,8]. Hereditary causes, mainly Lynch syndrome, are responsible for 3-5% of all EC cases. Women with hereditary cancer are generally younger.

The most common type of EC is endometrioid which develops from hyperplasia of the endometrium described according to Bokhman as the Type I pathway[9,10]. The risk factors for the development of the endometrioid type

are mainly associated to estrogen exposure, both endogenous through obesity, polycystic ovary syndrome and nulliparity and exogenous through substitution therapy with unopposed estrogen and tamoxifen in breast cancer treatment[11,12]. Less common are the non-endometrioid EC types developed in the Type II pathway described by Bokhman. Non-endometrioid EC arise in atrophic endometrium and is often a result of p53-mutation and high age is the main risk factor.

1.2 Symptoms and diagnosis

1.2.1 Symptoms

Postmenopausal bleeding is the most common symptom in EC, and it is usually an early symptom which allows for prompt detection in most cases. Disseminated disease at diagnosis is rare, but in such case the initial symptoms could also be related to the site of metastases, for instance abdominal pain and distension.

1.2.2 Diagnosis

In most cases the diagnosis is established in an outpatient setting at the gynecologist office. In the Nordic countries transvaginal ultrasound (TVUS) is a part of the regular routine gynecology exam. For the postmenopausal woman, an endometrial thickness of ≥5 mm in combination with bleeding raises suspicion of EC and a biopsy is recommended[13]. The endometrial biopsy is usually easily done with a good yield and reliable result with commercially available kits (Pipelle®, Endorette® etc)[14-16].

If cervical stenosis is present or other technical difficulties are present, then, a dilatation and curettage (D&C) or more preferable a hysteroscopy with biopsy should be performed. Hysteroscopy is considered the gold standard with a better accuracy than D&C[17].

Upon confirmed EC diagnosis, treatment planning is initiated which often includes a thoraco-abdominal computed tomography (CT) for metastasis screening or at least a chest X-ray for the low-risk cases. Local extension of tumor growth is assessed with TVUS or magnetic resonance imaging (MRI).

In endometrioid EC, metastases are uncommon but when they occur, the most frequent localizations are the regional lymph nodes. Hematogenous spread to the lung and locoregional metastases in the vagina or vulva may occur. Less frequent in endometrioid EC is carcinomatosis and parenchymatous spread to for example the liver or skeletal system.

In non-endometrioid EC, there is a higher proportion of disseminated disease at diagnosis than for endometrioid EC. Most common route of spread for non-endometrioid EC is to the regional lymph nodes and as carcinomatosis in the abdomen. Distant metastases are also more common than in endometrioid EC.

The finding on the biopsy of endometrial intraepithelial neoplasia (EIN), previously denominated hyperplasia with atypia, is considered a precancerous lesion to endometrioid EC and an indication for hysterectomy[18]. In 30-50% of EIN cases, there is already a developed EC at final pathology after hysterectomy[17].

1.3 Prognostic risk factors and risk classification

There are several prognostic indicators for risk of recurrence and survival to consider in the treatment of EC. For the preoperative planning of the extent of surgery, the risk factors for lymph node metastases are evaluated based on the diagnostic biopsy and imaging methods. After primary surgery, with the information of the final pathology, the risk factors guide the planning of optimal adjuvant treatment. The goal is to predict the risk of recurrence for the patient and individualize the recommended treatment, not to overtreat with unwanted side effects but neither to undertreat.

The evaluation of the importance of individual prognostic risk factors implies a challenge as new information is continuously evolving. Risk stratification schemes have been set up to guide in decision making in the preoperative setting and for adjuvant treatment. The basis for all risk stratifications is tumor histology, grade and stage. Tumor stage includes myometrial infiltration (MI), cervical stroma invasion (CSI) and lymph node status. In addition, lymph vascular space invasion (LVSI), age, tumor size and tumor molecular markers are considered in some risk stratifications. There are variations in the emphasis of risk factors in the classifications proposed; in

study protocols, national and international guidelines, and there have been changes evolving over time. An overview of the risk classification in Sweden, the present European guidelines, Mayo clinic criteria and two protocols of large and important EC studies is presented in *Table 1.*

Table 1. Summary of risk group classifications by selected guidelines and study protocols

Risk group	Swedish NGEC[19] 2017	European ESGO/ESTRO/ESP molecular class not known[20]	European ESGO/ESTRO/ESP with molecular classification[20]	PORTEC 1 study[21]	GOG-99 study[22]	Mayo criteria for low-risk[23]
Low	Preop: -EEC G1-2, MI<50%, no CSI Postop: -EEC G1-2, stage I-II -EEC G3, stage IA	-EEC G1-2, Stage IA and no LVSI	-Stage I–II POLEmut, no residual disease -EEC G1-2, Stage IA, MMRd/NSMP and no LVSI	EEC G1, Stage IA	-EEC G1-2 Stage IA with no MI	-EEC G1-2 with MI≤50%, and tumor diameter ≤2 cm -EEC all grades and tumor diameter with no MI
Intermediate	-	-EEC G1-2, Stage IB and no LVSI -EEC G3 Stage IA and no LVSI -NEC and no MI	-EEC G1-2, Stage IB MMRd/NSMP and no LVSI -EEC G3, Stage IA MMRd/NSMP and no LVSI -Stage IA p53abn and/or NEC, no MI	Stage I: -EEC G1, MI≥50% -EEC G2, any MI -EEC G3, MI<50%	-Age ≤50, EEC ≤2 risk factors* -Age 50–69 EEC ≤1 risk factors* -Age ≥70 EEC no risk factors*	-
High-intermediate	-	-EEC Stage I with LVSI -EEC G3, Stage IB -Stage II	-EEC Stage I MMRd/NSMP and LVSI -EEC G3 Stage IB MMRd/NSMP -EEC Stage II MMRd/NSMP	Age >60: -EEC G1-2 and MI ≥50%, -EEC G3 and MI <50%	-Any age, EEC 3 risk factors* -Age 50–69 EEC, ≥2 risk factors* -Age ≥70 EEC ≥1 risk factor*	-
High	Preop: -EEC G1-2, MI≥50% -EEC G3 -NEC Postop: -NEC -Stage III	-Stage III–IVA with no residual disease -NEC Stage I–IVA with MI and no residual disease	-EEC Stage III–IVA MMRd/NSMP no residual disease -EEC Stage I–IVA p53abn, with MI, no residual disease -NEC Stage I–IVA NSMP/MMRd, with MI, with no residual disease	-EEC Stage III–IV -NEC of any stage	-EEC Stage III–IV -NEC of any stage	-

Abbreviations: EEC= endometrioid endometrial cancer, NEC= non-endometrioid endometrial cancer, G1= FIGO grade 1, high differentiated EEC, G2= FIGO grade 2, intermediate differentiated EEC, G3= FIGO grade 3, low differentiated EEC, MI= myometrial infiltration, CSI= cervical stroma invasion, LVSI= lymph vascular space invasion, POLEmut= polymerase epsilon mutated, MMRd= mismatch repair deficient, NSMP= non-specific molecular profile, NGEC= National Guidelines for Endometrial Cancer, PORTEC= Postoperative Radiation Therapy in Endometrial Cancer, ESGO= European Society of Gynelogical Oncology, GOG= Gynecological Oncology Gruop (US)
**Risk factors: G2 or 3, LVSI, MI to outer third.*

1.3.1 Histology

The diagnostic biopsy gives a morphological diagnosis based on the histology and grade of the tumor. However, the preoperative diagnosis can be altered on the postoperative specimen, and this occur quite frequently. In a report by

Frumovitz *et al.*, preoperative International Federation of Gynecology and Obstetrics (FIGO) grade 1 or 2 was changed in 27% to 38% with an upgrading in 23-26%[24]. In a similar study, Leitao *et al*. found an upgrading of preoperative FIGO grade 1 in 14.7% and a change to serous or clear cell histology in 1.2% of the cases[25].

1.3.1.1 Endometrioid EC

Endometrioid histology constitute about 80% of all EC and yield a better prognosis than non-endometrioid. Endometrioid EC develops as a result of unbalanced estrogen stimulation of the endometrium, in the type I pathway according to Bokhman[9]. The endometrioid tumors are often of low grade, with diploid cells and hormone receptor positive for estrogen (ER) and progesterone (PR).

Tumor grade

Tumor grade is an independent prognostic factor for recurrence and survival[26]. According to FIGO, endometrioid EC is divided into three levels where grade 1 is highly differentiated, grade 2 moderately differentiated and grade 3 poorly differentiated tumor cells with specified pathological features[27]. In clinical practice, highly and moderately differentiated, FIGO grades 1 and 2, have similar risk profiles and are managed in the same way. A binary grading system has been proposed[28] and in the latest recommendation of the WHO classification of tumors[29], there is a dualistic division of the endometrioid EC into low-grade (FIGO grade 1-2) and high-grade (FIGO grade 3). The high-grade endometrioid constitute 15-20% of all endometrioid EC and behave more like the non-endometrioid and is sometimes referred to as the Type II in the Bokhman model[30].

1.3.1.2 Non-endometrioid EC

Approximately 15-20% of EC is of the non-endometrioid type and include serous cancer, clear cell cancer, carcinosarcomas and de-differentiated cancers. According to the Bokhman dualistic model they are referred to as Type II[9]. They have different traits regarding molecular biomarkers and varying underlying risk factors but have in common the more aggressive behavior compared to the endometrioid type. The prognosis is generally quite poor and non-endometrioid EC more often presents with metastatic disease at the time of diagnosis compared to endometrioid EC. The average age for patients with non-endometrioid EC is higher, the body mass index (BMI)

lower, multiparity more frequent and smoking more prevalent than for endometrioid EC[30]. Tamoxifen used for breast cancer is also a risk factor for development of serous cancer and carcinosarcoma.

Serous cancer is the most common within the group, followed by carcinosarcoma and the clear cell cancer type is the least common. Mutation of p53 is frequent (90%) in the serous cancer type and commonly found (60-90%) also in carcinosarcoma but more rarely in clear cell cancer (35%)[31].

1.3.2 Stage

Since 1988, the FIGO staging is surgical, following the postoperative pathology report incorporating lymph node status as well as depth of myometrial infiltration, cervical and adnexal involvement. The 1988 FIGO staging classification was based on reports of surgical-pathological risk factors and outcome correlations from the GOG-33 study[32,33]. The staging was revised in 2009 to be updated for a more accurate agreement of stage and prognosis[34]. The FIGO 2009 staging classification is displayed in *Table 2*.

Table 2. Endometrial cancer staging according to FIGO 2009

*FIGO Stage**	*Definition*
I	Tumor limited to the corpus uteri
IA	<50% invasion of the myometrium
IB	≥50% invasion of the myometrium
II	Tumor invasion of the cervical stroma
III	Tumor spread to local or regional structure
IIIA	Invasion of the uterine serosa and/or the adnexa
IIIB	Vaginal metastases and/or parametrial involvement
IIIC	Metastases to pelvic and/or para-aortic lymph nodes
IIIC1	Pelvic lymph node metastases
IIIC2	Para-aortic lymph node metastases
IV	Invasion of bladder or bowel mucosa, and/or distant metastases
IVA	Invasion of bladder and/or bowel mucosa
IVB	Distant metastases, incl. intra-abdominal. And/or inguinal lymph nodes

**Stages I-IIIB can include (i+) denoting presence of isolated tumor cells (ITC) in lymph nodes*

Tumor stage is a prognostic factor, with the best survival in the early uterine-confined stages. Most often EC is detected at an early stage as reflected in the overview of stage at diagnosis in Sweden shown in *Figure 3*. The dominance of early diagnoses accounts for the overall favorable prognosis in EC. *Figure 4* presents the RS per FIGO stage in the WSHCR for the years 2010-2020.

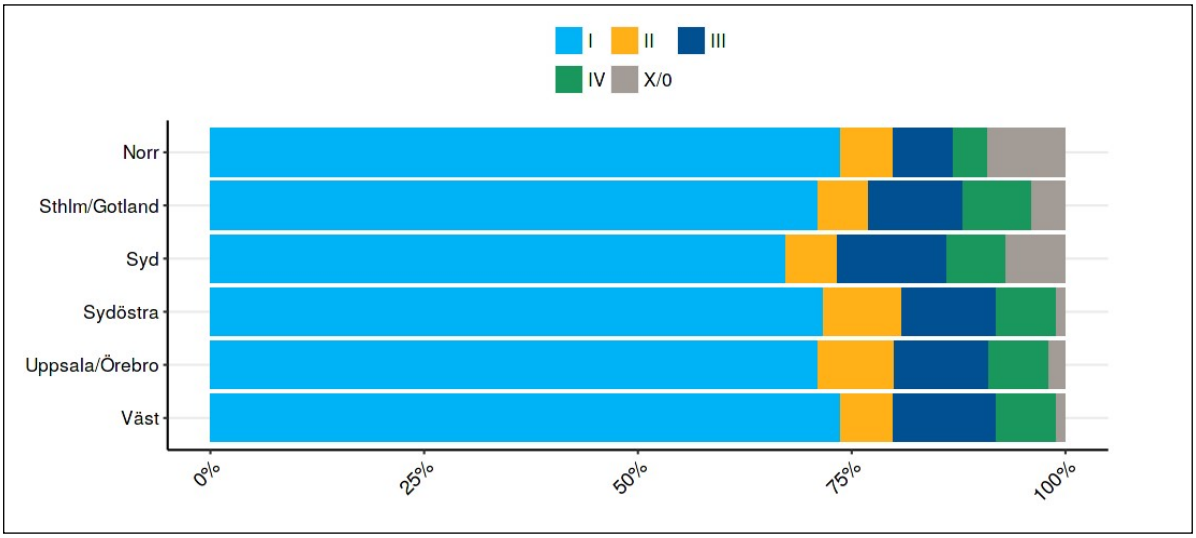

Figure 3. *Distribution of endometrial cancer FIGO stages in Sweden by region, data from the Swedish Quality Register for Gynecological Cancer 2010-2020. The Western Sweden Health Care Region (Väst) at the bottom.*

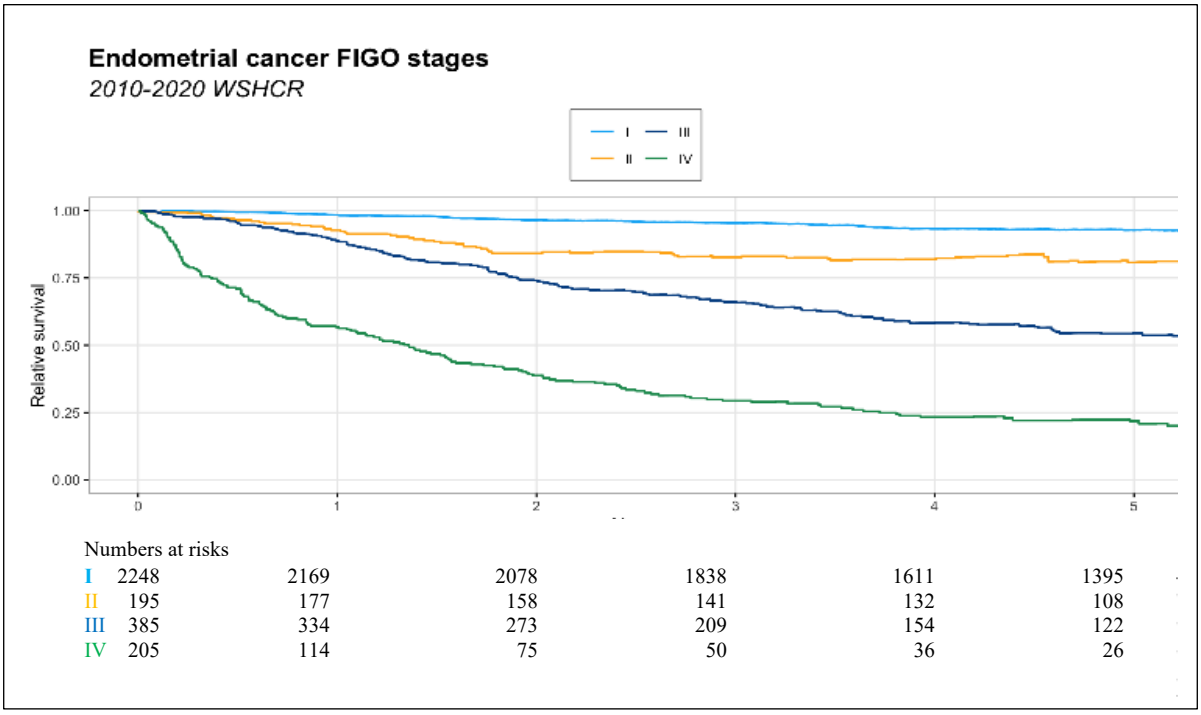

Figure 4. *Relative survival for endometrial cancer per stage in the Western Sweden Health Care Region (WSHCR) 2010-2020, data from the Swedish Quality Register for Gynecological Cancer.*

1.3.2.1 Myometrial infiltration

According to the FIGO 2009 staging classification, superficial MI, <50%, entails stage IA and deep MI, ≥50%, stage IB. Deep MI is a risk factor for lymph node metastases[31,36]. Since the final FIGO stage is set after the postoperative pathology report, there is a need to try to classify the presumed stage preoperatively in order to make the right decision about the extent of surgery. The preoperative assessment of MI is suggested to be done with MRI or TVUS and the modalities have shown a similar performance[37,38].

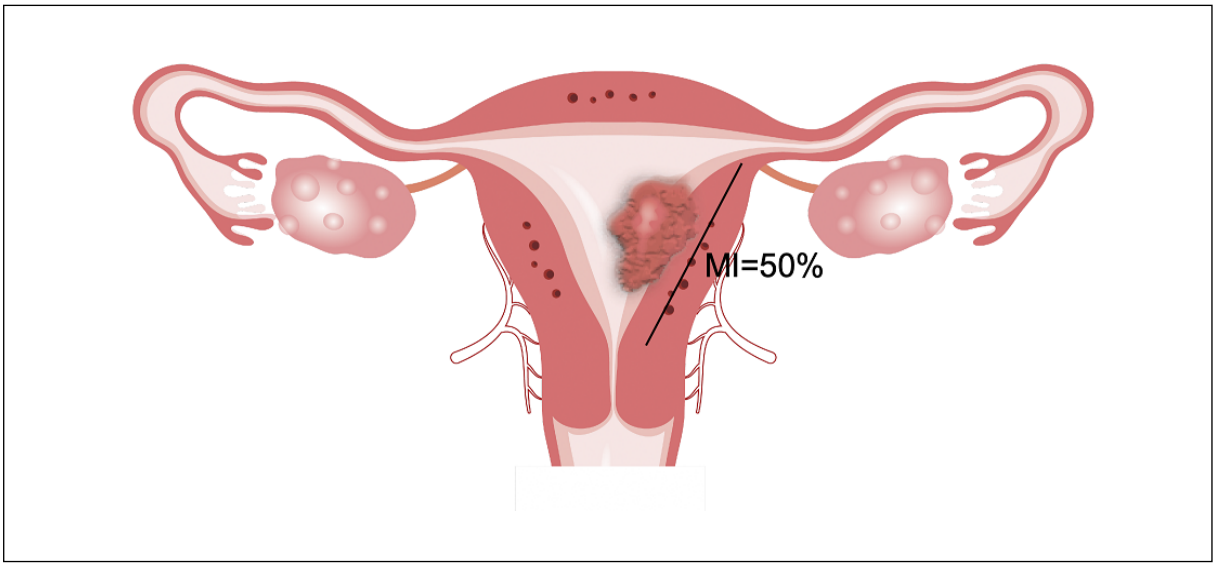

Figure 5. *Uterus with endometrial tumor, marking for 50% myometrial infiltration (MI). Illustration by Jan Funke*

1.3.2.2 Cervical stroma invasion

If the tumor extends from the uterine corpus into the cervix and infiltrates the stroma, the FIGO stage is II according to the FIGO 2009 classification. Cervical stroma invasion (CSI) is considered a prognostic risk factor, but superficial extension of the tumor in the endocervix, the former stage IIA according to FIGO 1988, is not[33,39]. The FIGO stage II is relatively uncommon (*Figure 3*). It can be questioned to what degree CSI is an independent prognostic factor as the prognosis seems to be favorable in this group in absence of other risk factors[40]. Lower uterine segment involvement, a feature possibly related to continued tumor growth into the cervix, has been considered a negative prognostic factor in some studies, but has not been confirmed as an independent risk factor[41].

It is quite rare for CSI to present as an obvious cervical tumor. In many cases, CSI is only detected microscopically at the post-operative pathological examination. Thus, CSI is not always possible to clinically diagnose preoperatively or reveal with imaging, where both MRI and TVUS provide a rather low sensitivity for detecting CSI. However, the preferred imaging method for detection of CSI is by many considered to be MRI, even though TVUS has shown similar results in some studies[42].

Surgery with radical hysterectomy by analogy with cervical cancer is not recommended because this has not shown superior results and is a more complicated procedure with a risk of morbidity[43,44]. In the rare cases of bulky tumor in the cervix, surgery should be performed to ensure a tumor-free surgical margin[20].

1.3.2.3 Lymph nodes

The presence of lymph node metastases render FIGO stage IIIC, where FIGO stage IIIC1 signifies pelvic nodal metastases and IIIC2 paraaortic.

The lymph drainage from the uterus and thus the endometrial tumor inside is mainly via the parametrium to the pelvic side walls: the obturator and iliac areas, and the presacral area. Additional lymphatic drainage from the uterus follows the ovarian vessels in the infundibulo-pelvicum ligament, to the paraaortic area above the inferior mesenteric artery and below the renal vessels. Pathological assessment of lymph nodes is necessary for complete surgical staging as preoperative imaging is at present insufficient to rule out lymph node metastasis. The lymph nodes are often not overtly enlarged, but contain occult metastatic spread, and thus are not possible to assess with ultrasound, CT or MRI. Positron emission computed tomography (PET-CT) has a higher accuracy of detecting lymph node metastases but reaches no more than 70% sensitivity[45-47]. Although the main routes of metastatic dissemination are in the pelvis, metastasis to the paraaortic area does occur. Creasman *et al*. reported a 4-6% risk of paraaortic node involvement in clinical stage I[32]. If the pelvic lymph nodes are positive, there is an almost 50% risk for positive nodes in the paraaortic area[48,49]. There is a variation in reported incidence of isolated positive paraaortic nodes, presumably depending on how meticulously the pelvic nodes have been examined. In recent studies the rate is as low as 1%[50].

In low-risk EC, defined by the Mayo criteria as low-grade endometrioid EC, with <50% MI and a tumor diameter of ≤2cm, the rate of lymph node metastasis was reported to be as low as <1%[23]. In high-risk EC the risk of lymph node metastasis can be as high as over 30%[32,51].

Lymphadenectomy

Lymph node assessment is generally not recommended in low-risk EC, but as histology and grade as well as stage are prone to change with definite pathology, the preoperative decision on low or high risk is challenging. The concept of sentinel lymph node evaluation has been proposed as a solution and this is further discussed below. With more upcoming information available on molecular markers, also in the preoperative setting, risk stratification and decision on lymph node assessment may get easier.

Full pelvic and paraaortic lymphadenectomy (PPLND) has been the recommended procedure to make sure metastatic lymph nodes are found. The numbers >10 pelvic and >5 paraaortic nodes harvested for a representative sample has been stipulated[19]. Surgery with lymphadenectomy is more complicated than only hysterectomy and bilateral salpingo-oophorectomy (BSOE) with a longer time of surgery and more complications. Additionally, there is a risk of development of long-term side-effects with lymphedema[52-55]. Due to these circumstances, the PPLND has been reserved for preoperative high-risk EC as a staging procedure to tailor adjuvant treatment[56].

Interestingly, there has been a controversy concerning if lymphadenectomy has a therapeutic effect, shown in some cohorts[57]. A large US register study of over 12000 patients showed an increased survival in the intermediate and high-risk group as a function of the number of nodes retrieved[58]. Furthermore, the SEPAL study showed in a retrospective cohort that paraaortic lymphadenectomy led to superior survival in comparison with only pelvic surgery, although this was questioned in the light that the postoperative treatment differed between the groups[59]. Furthermore, Eggemann *et al.* showed in a retrospective register-based cohort a superior survival in intermediate and high-risk group when PPLND was performed[60]. On the contrary, large randomized trials have not shown better survival following lymphadenectomy[61,62] and this was also what a Cochrane report concluded in 2017[63]. Moreover, isolated paraaortic recurrences have been shown to be unusual in patients with stage IIIC1 who had not undergone a paraaortic

lymph node dissection in the primary setting[64]. The current general consensus is that lymph node assessment is a staging procedure.

Sentinel node

The concept of the sentinel lymph node procedure is to pin-point the lymph nodes with the highest risk of metastasis and examine them meticulously with pathology ultra-staging, to set the stage with high precision and limited adverse effects. The efficacy of the sentinel lymph node procedure in EC has been evaluated in multiple studies[65-71] and has in the last few years been well established as the lymph node staging procedure for all EC including high risk EC[72,73,50]. The sentinel lymph node procedure is included as an alternative to PPLND for surgical staging in the updated European guidelines[20].

Anatomically, the lymph drains mainly parallel to the uterine vessels, pooled from the cervix and corpus, and it is logical that a cervical injection of dye works just as well as a laparoscopic fundal or peri-tumoral hysteroscopic injection. This has been shown in multiple studies[74,75]. There is evidence for the same pattern of lymphatic drainage for both cervical and endometrial cancer, likely favoring an anatomically based rather than diagnosis-specific lymphatic spread[76]. The possible disadvantage of the cervical injection would be that the para-aortic area is not mapped as well. Lymphatic drainage to this area is via the infundibulum-pelvicum ligamentum for which route the fundal injection performed better. Based on sentinel lymph node studies with pathology ultra-staging, isolated positive para-aortic lymph nodes are believed to be very infrequent, probably less than 1%, and may be considered negligible in this context.

Today, almost exclusively the fluorescent dye indocyanine green (ICG) is used as a tracer for the detection of sentinel lymph nodes. Blue dye and technetium isotope have been used in trials, but these agents have not been as successful as ICG related to difficulty in handling and lower detection rates[77,78]. When interstitially injected, the ICG uptake to the lymphatics is fast, within minutes, and stays in place for several hours, which is enough time to finish the surgical procedure. It is very easy to visualize the ICG in the lymphatics during surgery in near-infrared light which is available in the Da Vinci® robotic surgical system as well as other laparoscopic and open surgery systems.

Pathology ultra-staging refers to a multiple serial sectioning of the lymph nodes with Hematoxylin & Eosin (H&E) staining and usually with additional immune-histochemistry performed. This is in contrast to conventional evaluation of only a single H&E slide of the lymph node evaluated by the pathologist. This can be done in several ways and there is no consensus on a specified protocol[79]. Anyhow, pathology ultra-staging is a cornerstone of the sentinel lymph node concept and improves the detection of low-volume metastases that would otherwise have gone undiagnosed[80]. Low-volume metastases are micrometastases, consisting of tumor deposits of 0.2-2 mm, and isolated tumor cells (ITC), defined as <0.2 mm and less than 200 cells. It has been reported that almost 40% of lymph node metastases detected by ultrastaging were undetected on conventional pathology[79].

Algorithms for the sentinel lymph node concept have been presented, to make the procedure standardized and to achieve optimal results in terms of complete and accurate bilateral staging. The Memorial Sloan Kettering Cancer Center algorithm was the first to be introduced as a standard for the procedure[81]. Since 2020, all EC patients in Sweden are recommended staging with the sentinel lymph node concept following an algorithm with two different pathways depending on high- or low-grade histology of the tumor[8,82].

Some questions remain in the era of the sentinel node procedure for surgical staging in EC. The significance of micro metastases and ITC has not as yet been elucidated. There is some indication that prognosis is not worsened if ITC is detected in otherwise stage I-II endometrioid EC[83]. Another question is whether to proceed with paraaortic lymphadenectomy in the case of positive pelvic nodes as the risk can be as high as 50% for co-existing positive paraaortic nodes[50]. The paraaortic lymph node status is indicative in the planning of adjuvant treatment with extended radiotherapy fields.

1.3.2.4 Peritoneal cytology

Cancer cells found in peritoneal washings have been found a risk factor for recurrence, especially in the non-endometrioid histology. Han *et al*. found a recurrence rate of 87.5% in non-endometrioid EC with positive peritoneal cytology at primary surgery. However, in that study, 90% of the patients with positive cytology had other evidence of metastatic disease as well[84]. Positive peritoneal washing cytology has not been considered a strong individual

prognostic factor for survival and was omitted from the latest FIGO staging classification in 2009[34] .

1.3.3 Lymph vascular space invasion

The definition of LVSI is tumor cells appearing in lymph and blood vessels outside the border of tumor invasion[85]. It has been shown to be a risk factor for adverse prognosis in endometrioid EC[86,87]. When LVSI is present, it also predicts metastatic disease to the lymph nodes[88]. The drawback is that LVSI seldom is diagnosed in the preoperative setting, but on the postoperative specimen, which means that preoperative information for the judgement of extended surgery with lymph node assessment is lacking. Another weakness has been large interobserver variations between pathologists in the judgment on LVSI why the parameter has not been considered entirely reliable. In a pooled analysis of the Postoperative Radiation Therapy in Endometrial Cancer (PORTEC) 1 (1990-1997) and 2 (2002-2006) studies, there was a standardized approach to the decision on LVSI with three tiers: absent, focal or substantial LVSI . Only substantial LVSI should be considered an essential risk factor[89]. A prevalence of 4.8% for substantial LVSI in intermediate to high-risk EC was reported. The risk factor LVSI has thereafter been incorporated in the risk stratification in the European guidelines[20].

Even with negative lymph nodes, the trait of the tumor displaying LVSI seems to be associated with an increased risk of recurrence. Veade *et al.* showed a 20-fold increase for LVSI, from <1% to 18%, in nodal recurrences in endometrioid EC FIGO stage I with adequate lymph node dissection[90]. In a study of Ureyen *et al*., the rate of LVSI was 8.3% in FIGO stage 1A endometrioid EC, where the recurrence rate was 6.7% if LVSI was present and only 1% if not[91]. Substantial LVSI was associated with distant relapse and worse prognosis also in a study of Tortorella *et al.* in low grade endometrioid EC. In that study, 10.9% had any LVSI whereof 6.7% was focal and 4.2% substantial and the rate of distant relapse was increased from 1.8% for no LVSI to 22.7% for substantial LVSI[92].

1.3.4 Age

The prognosis in EC is negatively affected by higher age, corrected for age-related survival, histology type and stage[93].

1.3.5 Tumor size

The size of the tumor is a prognostic factor in endometrioid EC. Larger tumors are more prone to have deep MI and lymph node metastases[94]. Tumor size less than <2 cm is included in the Mayo clinic low-risk stratification of low-grade endometrioid EC[95]. For tumor size ≥2 cm, the recurrence rate increased from 1.3% to 11.2% in FIGO grade 1 stage IA EC, reported by Nwachukwu *et al.*[96]. In a multicenter French study, tumor size was found to be an independent risk for lymph node metastases only in low-risk endometrioid EC, with a cut-off at 35mm tumor diameter[97].

1.3.6 Molecular tumor biomarkers

In addition to traditional morphological classification of histopathology by type and grade, immunohistochemical techniques for assessment of tumor characteristics have been available for many years, supporting decision-making regarding high or low risk.

Immunohistochemistry is widely used for estrogen (ER) and progesterone receptor (PR) which, if positive, indicate low-risk disease. The result of ER and PR can be used to determine whether the use of hormone therapy can be effective in relapse or in a palliative primary setting. Analysis of the protein expression of the tumor suppressor gene p53 is used to distinguish high-risk type of tumors[98]. For example, the expression is often abundant in serous cancer. The L1 cell adhesion molecule (L1CAM) is proposed to be used together with ER/PR and p53 for a refined risk classification by Vrede *et al.*[99].

Furthermore, Mis Match Repair deficiency (MMRd) can be detected by immunohistochemistry of the expression of the mis match repair genes MLH1, MSH2, PMS2 and MSH6. The mechanism of MMRd is an inactivation of one MMR gene-allele that impairs a gene repair mechanism leading to so-called microsatellite instability (MSI). In 20-30% of EC, MMRd is present, of which approximately 10% are inherited mutations and the rest somatically derived mutations mostly MLH1 promotor methylation[100]. In addition to being a prognostic factor, MMR status is a treatment predictive factor. Tumors with high MSI are susceptible to immunotherapy treatment and recently there has been approval for immunotherapy in primary advanced and recurrent MMRd EC based on studies showing significantly prolonged survival[101].

The flow cytometry technique for cell nuclei DNA has been used to some

extent, for example in Sweden, as abnormal and unstable DNA of the cells can be a prognostic factor[102-104]. The diploid type resembles a normal cell and indicates low-risk and the non-diploid DNA type incur a higher risk. However, the ploidy status of the tumor cells has not been shown to be useful in the preoperative risk stratification because an independent association with lymph node metastasis has not been confirmed[104]. It was omitted as a risk factor from the Swedish National Guidelines for EC (NGEC) in the 2017 revision[19].

ProMisE

There has been rapid progress in recent years towards increased knowledge in the field of molecular biomarkers since the reporting of The Cancer Genome Atlas (TGCA) research in 2013[105]. Four distinctly different genetic subgroups of EC that correlate to survival were identified. These findings were further developed with surrogate molecular biomarkers into "the Proactive Molecular Risk Classifier for Endometrial Cancer" (ProMisE). The four groups are: Polymerase Epsilon Ultramutated (POLE), Mis Match Repair deficient (MMRd), p53 abnormal and non-specific molecular profile (NSMP)[106-109]. Several research groups have investigated and consolidated the ProMisE classification in clinical settings, so far mostly in retrospective analyzes of existing cohorts[110-117]. For the POLE-mutated tumors, which represent 6-9%, the prognosis is excellent, although the conventional histology often shows worrisome features. The p53 abnormal tumors often have serous histology and constitute about 15% of all EC. They are aggressive in nature with poor prognosis. Between 20-30% of all ECs are MMRd with an intermediate prognosis. Nearly half of the ECs are grouped in the NSMP, where the prognosis is on average intermediate, but varying. This new molecular classification system for EC has been incorporated in the latest edition of the pathology "Bible", the fifth edition of the WHO Classification of Female Genital Tumors[29,118] and is integrated into the risk stratification of the latest European guidelines for EC[20].

Some of the ProMisE biomarkers can be analyzed through commonly used conventional immunohistochemistry methods. This applies to p53 and MMR described above although not POLE, for which molecular genetic analysis is required. Currently, the new methods with molecular genetic analyses and next generation sequencing are being built up to be available in a wider context so that the full potential of the ProMisE classification can be reached.

1.4 Lynch syndrome

The Lynch syndrome entails the greatest portion of hereditary causes for EC, causing around 3% of all EC. The syndrome is named after Henry T. Lynch (1928-2019) who discovered the autosomal dominant genetic trait that causes several cancers, most commonly colorectal and endometrial cancer. In the pooled cohorts of PORTEC 1, 2 and 3 trials, the prevalence of Lynch syndrome was 2.8%. In the presence of MMRd tumors, the prevalence was 9.5%[100]. Most of the MMRd tumors are not caused by Lynch syndrome but a result of sporadic acquired somatic defects of the MMR gene. In any case, the finding of MMRd in EC is in many cases an indication for further genetic investigation for the Lynch syndrome. It is beneficial for the individuals and their families to be informed about the hereditary Lynch syndrome because there is effective surveillance to either early detect or prevent both endometrial and colorectal cancer.

1.5 Primary Treatment

1.5.1 Surgery

Primary treatment for EC is surgical with hysterectomy and BSOE as baseline treatment. Lymph node dissection or sentinel lymph node procedure for surgical staging is added in the high-risk groups as discussed above. Omental biopsy is recommended in non-endometrioid EC. A majority of the patients go through primary surgery, including the older and less fit patients, which is a benefit of the evolvement of minimal invasive surgery (MIS), especially robotic surgery.

1.5.1.1 Surgical techniques

The oncological safety of MIS has been confirmed in the randomized LAP 2 and LACE trials[119,120] and also reassured in high risk EC[121]. The further development with robotic surgery has enabled the more complicated EC surgery, including lymphadenectomy, to be performed minimally invasive. In the case of overt extrauterine disease in the abdomen the preferred surgery is by open surgery, to be able to perform cytoreductive surgery according to the same principles as for ovarian cancer surgery[122].

1.5.1.2 Special considerations in EC surgery

There are many elderly patients in the EC population and quite a few with intercurrent diseases and obesity. A study at our institution showed that robotic surgery was feasible also in the elderly population regarding surgical complications and oncological outcomes[123]. Some authors have proposed a standardized frailty index for the prediction of complications and worse outcomes in EC[124,125].

Charlson´s comorbidity index

Charlson´s comorbidity index was first developed by following a cohort of patients with medical conditions and assigning scores to the risk of one-year mortality. The purpose was to make a scoring system of comorbid conditions for prediction of risk of mortality to be used in longitudinal studies[126]. An adaptation of the Charlson´s index was done with the combination of age for the estimation of risk of death in the context of perioperative complications[127]. The use of the comorbidity score is suggested in studies of EC surgery[126-128] to evaluate the perioperative risks in patients with multiple comorbidities. The Charlson´s comorbidity index is shown in *Table 3*.

Table 3. Charlson´s comorbidity index

Score	Medical condition
1	Myocardial infarction Congestive heart failure Cerebral vascular disease Peripheral vascular disease Dementia Chronic obstructive pulmonary disease Connective tissue disease Peptic ulcer disease Mild liver disease Diabetes
2	Hemiplegia Moderate or severe renal disease Diabetes with end organ damage Any tumor Leukemia Lymphoma
3	Moderate or severe liver disease
6	Metastatic solid tumor AIDS

The number is the weight for each condition and the total equals the score. For age-adjusted score, +1 per decade after 40

Obesity

Obesity, defined as BMI ≥30[129], is a common trait in EC patients as this is a major risk factor for the development of endometrioid EC. This is a challenge in surgery as the obese habitus restricts access for the surgeon in the operating field but also causes impaired wound healing with a higher rate of infections and seromas. There is an advantage for MIS compared to open surgery in the obese as the access is improved and entry wounds are smaller and thereby heal better. Conventional laparoscopy can be a challenge in the obese. The robotic system offers easier positioning and access in comparison and thereby lower conversion rates[130]. The safety of robotic surgery in obese EC patients has been evaluated and although more complications occur than in the non-obese there is still an advantage compared to complication rates for open surgery[131-133].

1.5.1.3 Surgical complications

Complications to surgical procedures, that is unwanted deviations from the expected perioperative course and postoperative recovery, should be minimized. Surgical complications can inflict the burden and pain of a prolonged recovery. In the worst case, complications can result in long-lasting or permanent disabilities for the patient or even death. In cancer surgery, surgical complications may imply a risk of delayed or inhibited adjuvant treatment possibly interfering with the outcome.

Clavien-Dindo classification of surgical complications

Classification systems of complications are used in surgical publications to get an overview of complications and the associated severity of the complications. A publication in 2004 proposed a five-grade grading system which was a development of an earlier grading system published in 1992[134,135]. This Clavien-Dindo classification scoring system has won ground and is widely used in many surgical specialties and comparisons can be performed between cohorts. The Clavien-Dindo grading system is displayed in *Table 4* with examples from EC surgery. Another modification of the complication system is called the MSKCC Severity Grading of Surgical Complications or Martin criteria which also stipulate quality criteria for the reporting of surgical complications[136]. One of the authors of the original 1992 classification system has made further developments of the system in the Accordion Severity Grading System, with the aim to make it easier to use[137].

Table 4. Clavien-Dindo classification of surgical complications

Grade	Definition[138]	Examples in EC surgery (derived from Paper III)
I	Any deviation from the normal postoperative course (allowed: antiemetics, analgetics, diuretics, electrolytes, physiotherapy, superficial wound infection opened bedside)	-Vaginal or wound lymphatic leakage -Superficial wound infection -Sensory nerve affection -Hematoma or vaginal bleeding
II	Requiring pharmacological treatment, blood transfusion or parenteral nutrition	-Blood transfusion -Urinary tract infection -Wound infection -Vaginal vault or abdominal infection -Pneumonia -Venous thromboembolism -Cardiac atrial fibrillation
III	Requiring surgical, endoscopic or radiological intervention	
IIIa	Not under general anesthesia	-Vaginal vault abscess, drainage -Residual urine, suprapubic catheter
IIIb	Under general anesthesia	-Wound dehiscence -Bowel obstruction -Urinary tract injury
IV	Life-threatening complication	
IVa	Single organ dysfunction (incl dialysis)	-Pulmonary embolism, intensive care -Pulmonary failure, intensive care -Myocardial infarction
IVb	Multi organ dysfunction	
V	Death	

Surgical complications are often reported in surgical studies but rarely as primary outcome. The interest for surgical complications in EC in the last decade has pointed towards comparisons between open surgery, MIS and robotic surgery, where the latter has been found to be beneficial especially in frail patients and patients with a high BMI.

1.5.1.4 Lymphatic complications

Lymphedema in the lower limbs can be considered a long-term complication of lymphadenectomy surgery and it is associated with significant impairment of quality of life[139]. In reports on lymphedema, the incidence varies greatly from 0 to 50% and maybe the true estimate is somewhere in the middle. Nonetheless, in long term cancer survivors, the long-term side effects of the treatment must be seriously considered and avoided if possible. In a single institution retrospective study of 249 patients by Volpi *et al.*, the rate of postoperative leg lymphedema was as high as 36.9% and the rate of

lymphocele 17.3%. Patients having had paraaortic lymphadenectomy were at the greatest risk[55]. The extent of lymph node surgery is probably one of the predictors of the risk for lymphedema where dissection distal to the circumflex vein have been associated with increased risk for leg lymph-edema[140]. Surgical technique, with open or robotic surgery, for lymphadenectomy does not appear to affect long-term lymphatic complications[141]. Our institution participated in a Swedish multicenter study with a prospective observational design, the Lymphedema After Surgery for Endometrial Cancer (LASEC) study. The study evaluated lymphedema in EC surgery for patients having surgery with and without lymphadenectomy, pelvic or pelvic and paraaortic. In this study, lymphedema and lymphocele development were evaluated both by objective methods with standardized leg measures, clinical grading and TVUS and subjective methods through patient questionnaires at baseline, postoperative at 1, 6 and 12 months. Results from the LASEC study showed a variation in lymphedema incidence depending on method of assessment. Leg measurement showed a rate of 15.8% after lymphadenectomy and 3.4% without lymphadenectomy, at one year. The corresponding patient reported rate was 10.7% and 5.1% and for clinical grading 24.1% and 11.8%. Analyses for risk factors were undertaken and were shown to differ in relation to the methods of assessment. Furthermore, quality of life was affected in the lymph-related domains but not on a general level[52-54].

1.5.2 Adjuvant treatment

The evidence for adjuvant treatment in EC is scarce as valid data is still lacking. There is no general consensus regarding adjuvant treatment for EC in FIGO stage I and therefore there is a variation of recommendations in guidelines worldwide.

1.5.2.1 Radiotherapy

Adjuvant external beam radiation therapy (EBRT) and vaginal brachytherapy (VBT) have been part of the adjuvant treatment in EC for many years. This has resulted in side effects for a large population of long-term EC survivors. Discussions are ongoing as how to best chose the EC patients that benefit from treatment as to spare the rest the unwanted side-effects on urinary bladder, colon and intestines and also the risk of secondary cancers[142]. Radiotherapy has been proven to be effective in reducing locoregional recurrences, but has not shown improved survival in EC FIGO stage I. Furthermore, the survival

after relapse is better in the primarily non-radiated patients. This was concluded in the first PORTEC study[143,144] and the recommendation was to limit radiation to patients with a high risk of recurrence in stage I and to patients with residual disease. The finding of better locoregional control but no improved survival was also found in the intermediate risk group studied in the US GOG-99 trial and their conclusion was to recommend radiotherapy only to the high-intermediate and higher risk groups[22].

Low-risk EC should not receive adjuvant radiotherapy. A Danish study showed a 96% survival rate in this group[145]. Likewise, a Norwegian study show no improved survival with adjuvant radiotherapy in stage I[146].

The second PORTEC study showed in stage I with high or intermediate risk factors equal effect of only VBT compared to EBRT for local control[147,148]. The VBT gave less long-term complications than EBRT and follow-ups showed an improved quality of life. Hereafter the mainstay became to give only VBT instead of EBRT+/-VBT in the adjuvant setting in FIGO stage I. In Denmark, the de-escalation of radiation has gone further after Ortoft *et al.* showed maintained survival rates without any radiation in the high/intermediate risk group, although more recurrences were seen[149].

1.5.2.2 Chemotherapy

Adjuvant chemotherapy in EC is used in high-risk stage I-II EC and for stage ≥III EC, alone or in combination with radiotherapy. The drugs used are most often a combination of paclitaxel and carboplatin. Efficacy of only chemotherapy, without radiotherapy for stage I EC with high-risk features remains to be elucidated. Results of a randomized study on this is expected in the near future (ENGOT-EN2-DGCG/EORTC 55102). Adjuvant chemotherapy was equivalent to radiation in the adjuvant setting for high- and intermediate risk EC in studies by Maggi *et al.* and Susumu *et al.*[150,151]. The combination of radiotherapy with addition of chemotherapy has been shown to be more effective than only radiation in the high-risk group (high grade endometrioid and non-endometrioid) in a study with pooled data from NSGO-EC-9501 /EORTC-55991 and MANGO ILIADE-111[152].

In the US study GOG 249, chemotherapy was better than radiation in advanced stages, stage III and IV[153]. In another US study, the GOG 258, there was no

difference in survival for patients receiving only chemotherapy compared to chemotherapy in combination with radiotherapy in advanced stages[154].
The third and most recent published PORTEC study, was a randomization for adjuvant therapy in high-risk EC, with adjuvant radiotherapy alone or in combination with cisplatin and followed by four cycles of paclitaxel and carboplatin. The prognosis was superior for stage III patients if chemotherapy was given in combination with EBRT compared to only EBRT[155]. This finding is the ground for the current recommendations of combined adjuvant treatment in FIGO stage III[8,20].

1.5.2.3 Other treatments
There are no current recommendations in EC for additional targeted treatments in the adjuvant setting. However, there are studies ongoing investigating checkpoint inhibitors, immunotherapy and hormonal treatment in relation to molecular biomarkers. A large study, Refining Adjuvant treatment In endometrial cancer Based On molecular features (RAINBO), is currently recruiting (https://clinicaltrials.gov/ct2/show/NCT05255653).

In the advanced stages and recurrent setting, immunotherapy can be a good option and has recently been approved[101,156]. There are further ongoing studies, for example the RUBY study (https://clinicaltrials.gov/ct2/show/NCT03981796).

For the inoperable patients with low-grade ER- and PR positive tumor, gestagen treatment can be an alternative for disease control, either administered as high dose peroral or as hormone-releasing intrauterine device. The same regimens can be used to suppress very early low-grade EC for fertility-sparing purpose in younger women.

1.6 Recurrence

The occurrence of recurrence may be assumed to be an event of occult residual disease after primary treatment. The disease was either not revealed at the surgical staging or did not resolve with the adjuvant treatment. The risk of recurrence depends on risk factors of the tumor, with high-risk tumors apparently having a higher risk of recurrence than low-risk, but there are still unanswered questions regarding risk factors for recurrence.

Reported recurrence rates vary in the literature, as case mixes differ. In cohorts with a supposed average representation of EC types, the total recurrence rates is reported to be 13%-21%[157-159]. Studies show recurrence risks from 3.4% in a very low-risk cohort[91] to 28-40% in high-risk cohorts[149,157,160].

Most recurrences appear in the first years after diagnosis with reported range of 65-85% occurring within 3 years from primary treatment[158,161].

The recurrences can be locoregional, in the vaginal vault or pelvis, in the lymph nodes, as carcinomatosis in the abdomen or at a distant site. The sites of recurrence seem to vary based on the primary tumor characteristics. In general, locoregional recurrences in the pelvis or vaginal vault are reported to be more common in low-intermediate risk and distant or disseminated recurrences are more common in high-risk[26,84,149,160,162,163].

1.6.1 Recurrence treatment

A localized relapse can be cured. Surgery is an option[164]. Radiation is effective for recurrences localized to the vagina or confined to the pelvis but can only be given if it has not been received in the primary setting[165,166].

In case of disseminated or distant recurrence and in the case surgery or radiation is not an option, chemotherapy is considered. In those situations, the recurrence is rarely curable. Treatment with antihormonal agent or gestagens can be an option if ER and PR are positive.

A new emerging possibility for the MMRd tumors in the recurrent setting, is immunotherapy, which have been shown more effective than chemotherapy[167] and further studies are ongoing.

1.7 Follow-up

Recurrences are symptomatic in 75%, while 25% are asymptomatic, but with the same survival rate[168]. In this context, the regular follow-up after EC treatment can be discussed.

Currently most EC patients are recommended regular clinical follow-up. An argument of the follow-up of non-radiated patients is that early detected vaginal relapse may be cured[169]. The stipulated follow-up is based on clinical examination and evaluation of symptoms to guide further investigation with biopsy and radiology. Pap smears or routine radiology have not been shown to be effective in detecting recurrence[170,171].

On the other hand, routine regular follow-up in stage I endometrioid EC has been questioned by some based on findings of recurrences being symptomatic and not identified on planned follow-up visits[172]. It has not been proven efficient with an extensive control program in low risk EC as a very low number of asymptomatic recurrences are discovered[173].

A requirement for the strategy to skip planned follow-up visits would be to have well-informed patients and an easy access to care when symptoms appear. Strategies similar to that has been proposed by several authors[174,170,175].

1.8 Survival

In general, the survival rates in EC are favorable. This is mainly due to early diagnosis, when the disease is confined to the uterus. When there is no metastatic disease, the overall survival range from 74-91%[31].

The survival is highly affected by recurrences and is dependent on the extent and the site of recurrence where patients with isolated vaginal recurrences have a reported survival of 64-73% compared to 14-17.5% in distant[144,176]. Furthermore, it has been shown that patients with pelvic recurrences have longer survival than with extra-pelvic and that radiation naïve patients have longer survival following a relapse[177]. The survival after relapse depends on the possibility to reach the recurrence with treatment, radiation or surgery[178]. *Figures 6* displays the 5-year RS in the WSHCR for the total cohort, the cohort of only the patients that had primary surgery and the cohort with surgical treatment and stage I-III.

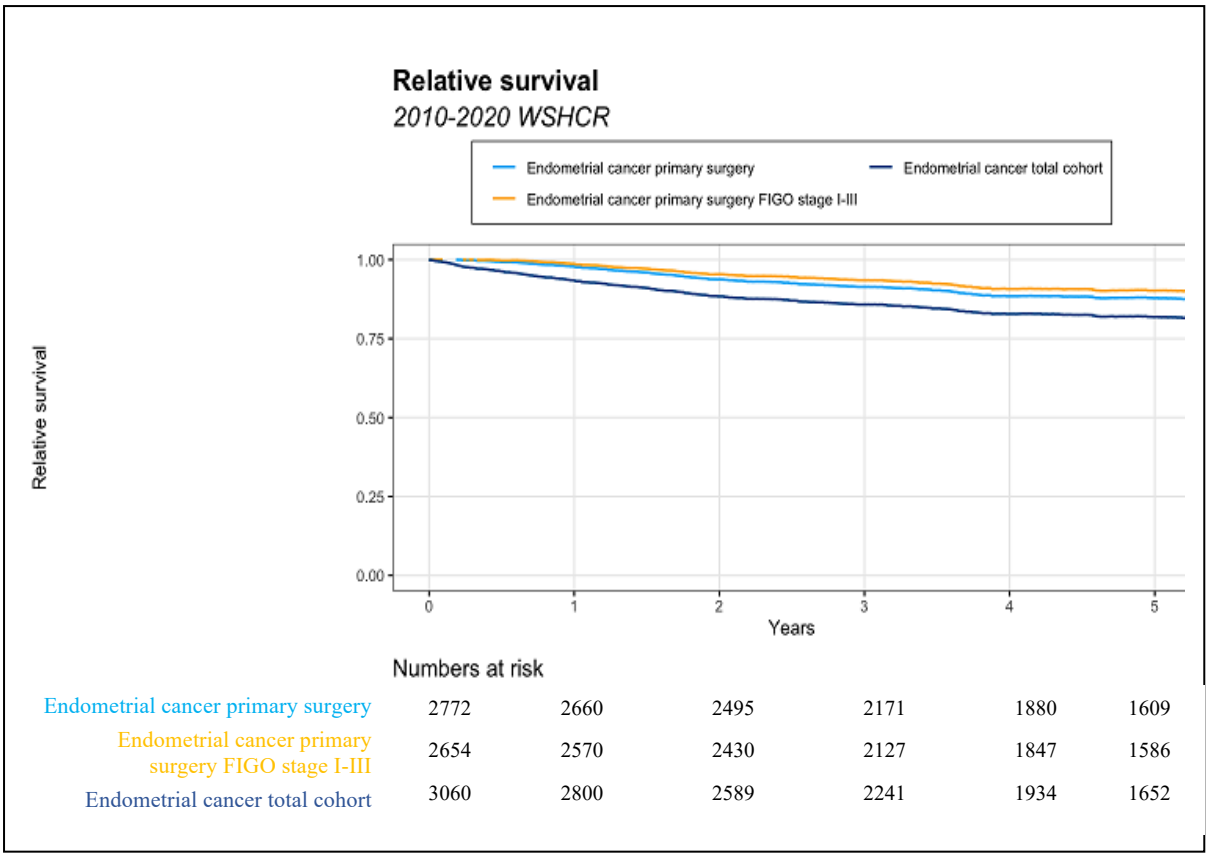

Figure 6. *Relative survival for Endometrial cancer: total cohort, only patients with primary surgery and patients with primary surgery, only stages I-III, in the Western Sweden Health Care Region 2010-2020. Data from the Swedish Quality Register for Gynecological Cancer.*

1.9 Swedish Quality Register for Gynecological Cancer

Sweden has a long history of complete registers. Since 1947, all inhabitants are designated a personal identification number which have made registers connected to individuals possible. The National Cancer Register (NCR) was introduced in 1958 as the first health care register. Registration of all cancer cases in the NCR is mandatory. The National Death Register (NDR) is in place since 1950. The NCR consists only of baseline data connected to the cancer diagnosis, such as date of diagnosis, and in conjunction with the NDR, survival can be calculated. A need for more data on the specific cancer diagnoses was identified and in the late seventies Regional Oncologic Centers were established to monitor cancer diagnoses and regional tumor quality registers were developed. In 2006, a cooperation between the regions was initiated after a decision by the government and the national health administration. The intention was to conform the standard of cancer care in Sweden with national

instead of regional guidelines[179]. The regional registers were to be made equal for the possibility of easier access to comparable national data. Regional Cancer Centers at the six medical regions of Sweden with a national coordination evolved. A web-based register platform called INCA was developed and was launched in 2007.

For gynecological cancers, the register was named the Swedish Quality Register for Gynecological Cancer (SQRGC), and ovarian cancer was the first diagnosis to start in 2008. Endometrial cancer followed in 2010. In the WSHCR registration has been very complete since the beginning with nearly 100% coverage towards the NCR. Detailed information on patient and tumor characteristics, surgery, adjuvant treatments, surgical complications, oncological outcomes and data on follow-up for five years are included in the register. The registration in the SQRGC is prospective and undertaken consequently by the treating gyneoncological surgeons and gyneoncologists. There is a regular daily connection to the NDR for accurate information on the vital status of the patients. The validity of the register has been evaluated with high conformity of the variables. In a national study re-abstracted data for 250 EC patients were compared to the SQRGC for the years 2010-2011 and 2014-2015. The completeness towards the NCR was 96% and the median agreement on core variables was 82.1%[181].

1.10 Summary

The outcome of EC is affected by recurrence and surgical complications. Although there are many studies on EC it is difficult to make valid comparisons due to patient selection in institutional studies with different case mixes and treatments given. Population-based studies with robust data are scarce. There is a need for data emanating from a complete population and in the regional setting of the WSHCR we have a good opportunity to perform studies through the valid register SQRGC. Furthermore, there is still a need for optimal preoperative assessment for the decision making on risk group classification in low-grade EC, with the goal not to misclassify and risk over- or undertreatment.

2. Aim

The overall aim of this thesis was to study recurrence, survival and surgical complications in a complete population-based cohort of EC patients related to the introduction of NGEC recommending PPLND in high-risk EC. A second aim was to evaluate preoperative risk classification with TVUS and MRI in low-grade endometrioid EC.

2.1 The specific aims were:

- To explore recurrence rates and patterns in endometrioid (Paper I) and non-endometrioid EC (Paper II)
- To investigate prognostic factors for recurrence (Paper I)
- To study overall, relative and disease-free survival (Papers I, II and III)
- To study survival in endometrioid EC related to grade and stage (Paper I)
- To study the impact of recurrence and recurrence localization on survival (Papers I and II)
- To assess effects of the implementation of the first NGEC on recurrence and survival (Papers I and II)
- To analyze risk factors for surgical complications and explore complications in relation to the implementation of NGEC (Paper III)
- To assess survival in relation to surgical complications (Paper III)
- To explore if TVUS performed by gynecologists with a brief training is comparable to MRI for the assessment of deep MI and CSI as the first line modality for decision making on preoperative risk classification in low-grade EC (Paper IV)

3. Patients and methods

All four Papers were carried out in the WSHCR. The SQRGC was used for extraction of data for Paper I-III and Paper IV was a prospective multicenter study. The scope of all studies was to investigate preoperative early-stage EC. Therefore, in the following description of patients and methods, the patients with disseminated disease at diagnosis are not discussed further. *Table 5* displays an overview of the patients and methods in the studies.

Table 5. Overview of Patients and Methods

	Paper I	**Paper II**	**Paper III**	**Paper IV**
	Population-based register cohort study	Population-based register cohort study	Population-based register cohort study	Prospective multicenter study
Setting	WSHCR	WSHCR	SUH	WSHCR
Data source	SQRGC, medical records	SQRGC, medical records	SQRGC, medical records	PODEC study protocol
Number of patients	1630	228	556	259
Period of inclusion	2010-2017	2010-2017	2012-2016	2017-2019
Statistical methods	Descriptive, Kaplan Meier, Competing risk analysis, SHR regression	Descriptive, Kaplan Meier, Cox regression	Descriptive, Kaplan-Meier, binary logistic regression, Cox regression	Diagnostic accuracy, Cohens kappa, Mc Nemar
Outcomes	Recurrence description, OS, NS, DFS, CIF, SHR	Recurrence description, OS, DFS, HR	Complications description, OR, HR, OS	Sensitivity, specificity, PPV, NPV, Interreader agreement

Abbreviations: WSHCR= Western Sweden Health Care Region, SUH= Sahlgrenska University Hospital, SQRGC= Swedish Quality Register for Gynecological Cancer, PODEC= PreOperative Diagnostics of low-grade Endometrial Cancer, OS= Overall Survival, NS= Net Survival, DFS= Disease-free Survival, CIF= Cumulative Incidence Function, PPV= Positive Prognostic Value, NPV= Negative Prognostic Value, TVUS= Transvaginal ultrasound, MRI= Magnetic Resonance Imaging, SHR= sub distribution hazards ratio, HR= hazard ratio, OR= odds ratio

3.1 Setting

3.1.1 The Western Sweden Health Care Region

The WSHCR with around 1.9 million inhabitants comprises about a fifth of the Swedish population and there are almost 300 new cases of EC per year. The Region Västra Götaland (VGR) constitutes the largest portion of the WSHCR, which also include the northern part of the Region Halland. Involved in the care of EC patients are the tertiary center, the Sahlgrenska University Hospital (SUH) in Göteborg, and four county hospitals: NU Hospital in Trollhättan, Skaraborg Hospital in Skövde, Södra Älvsborg Hospital in Borås and Varberg Hospital.

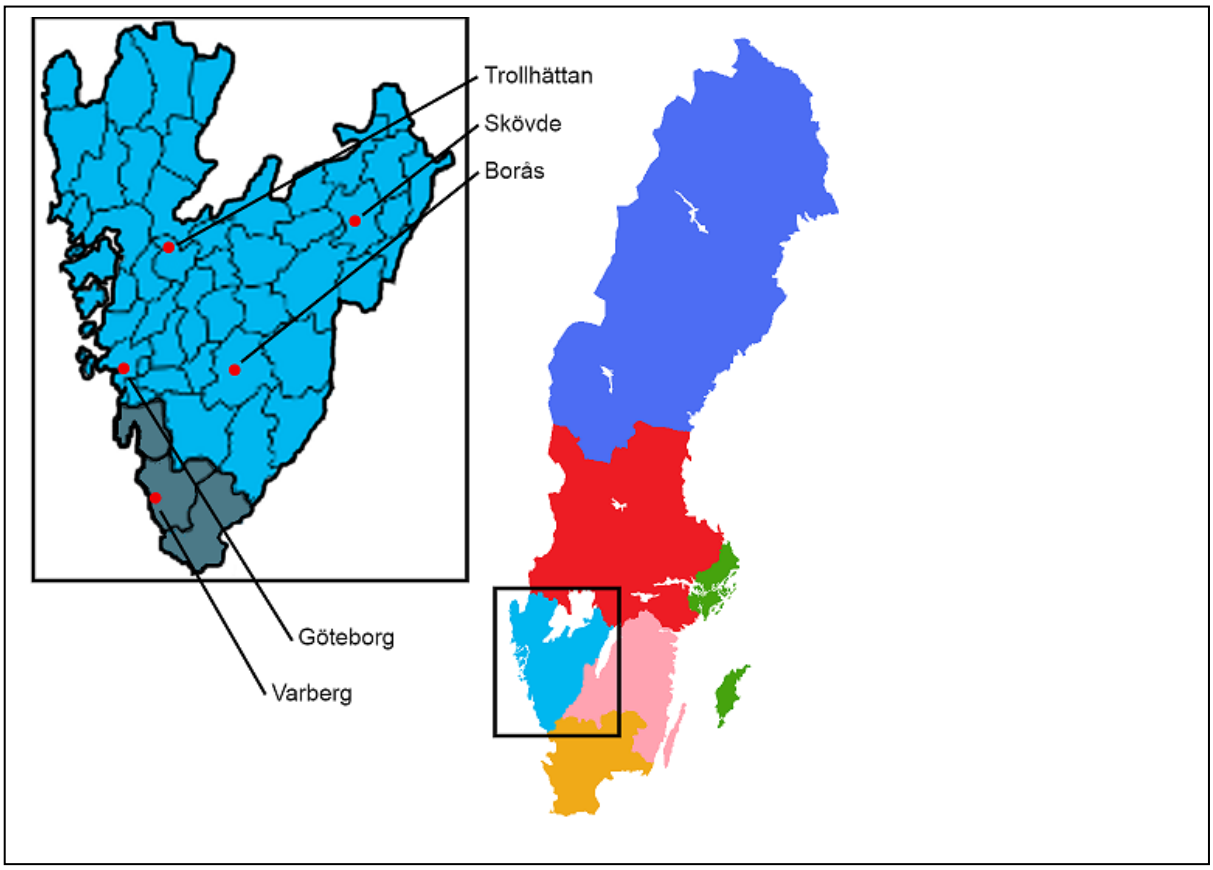

Figure 7. *Map of Sweden with the six health care regions. The magnified map displays the Western Sweden Health Care Region (WSHCR), Region Västra Götaland in light blue and Northern Halland in grey.*
Map from: file:///wiki/File:SWE-Map_Sjukvårdsregioner.svg
https://en.wikipedia.org/wiki/en:Creative_Commons. Modifications made by Erik Åkesson.

A major part of gynecological cancer surgery is centralized to tertiary centers in Sweden. For vulva cancer there has been a national centralization since 2017 and for the other gynecologic cancer diagnoses there has been a regional centralization

to various extent. Radical hysterectomy has been centralized for decades and advanced ovarian cancer surgery for more than ten years. The evolvement in EC surgery also involved a centralization and is further described below. At SUH there is a team of subspecialized gyne-oncology surgeons, accredited by the Swedish society for Obstetrics and Gynecology (SFOG), and at the county hospitals there are general gynecologists with interest in gynecologic cancer care. The subspecialist gyne- oncology surgeons at SUH work only with gynecologic cancer patients and perform surgery for endometrial, ovarian, cervical, and vulvar cancers, but do not treat or decide on chemotherapy or radiation protocols. There are medical and radiation gyne-oncology specialists at SUH that decide and perform all adjuvant treatments for the patients in the Göteborg area, and the radiation treatments for all patients in WSHCR as well as supervising the chemotherapy at the county hospitals. The actual treatment cycles of chemotherapy are prescribed by the gynecologists at the county hospitals and administered by oncology trained nurses. The gynecologists at the county hospitals perform surgery in some of the gynecological cancer cases after decision-making at regional multidisciplinary treatment boards (MDTs). The teams at the county hospitals work closely with the tertiary center on a daily basis and also participate in diagnosis specific cancer process groups with regular meetings working with updated treatment protocols together with taking part in the development of the gynecological cancer care.

In Göteborg and the adjacent suburban area there are around 20 outpatient gynecology clinics where the majority of EC patients are diagnosed and then referred to SUH for treatment. The Göteborg area comprises almost half of the population of the WSHCR and thereby the corresponding portion of EC patients. In the rest of the region, most of the gynecology outpatients are handled at the county hospitals and the EC patients thus are diagnosed within the hospitals.

3.1.2 Swedish quality register for gynecological cancer

The registration of EC in SQRGC started in 2010. In the WSHCR the registration has been comprehensively complete from the start due to a meticulous monitor function at the Regional Cancer Center West. The SQRGC coverage towards the NCR was 99.8% for 2010-2020. In the WSHCR the internal coverage for the surgery form was 99.7% and the post-treatment form 99.8%. Registration is carried out by the treating physicians prospectively and continuously along the path of the patient´s treatment. The patients are informed of the registration in SQRGC at the preoperative visit and rarely decline participation.

3.1.3 Treatment guidelines

During the time period covered by this thesis, treatment guidelines changed on two occasions, as presented in the timeline in *Figure 8.*

Before the first NGEC were established there were regional guidelines. The goal with national guidelines was to make the treatment equal regardless of place of residency.

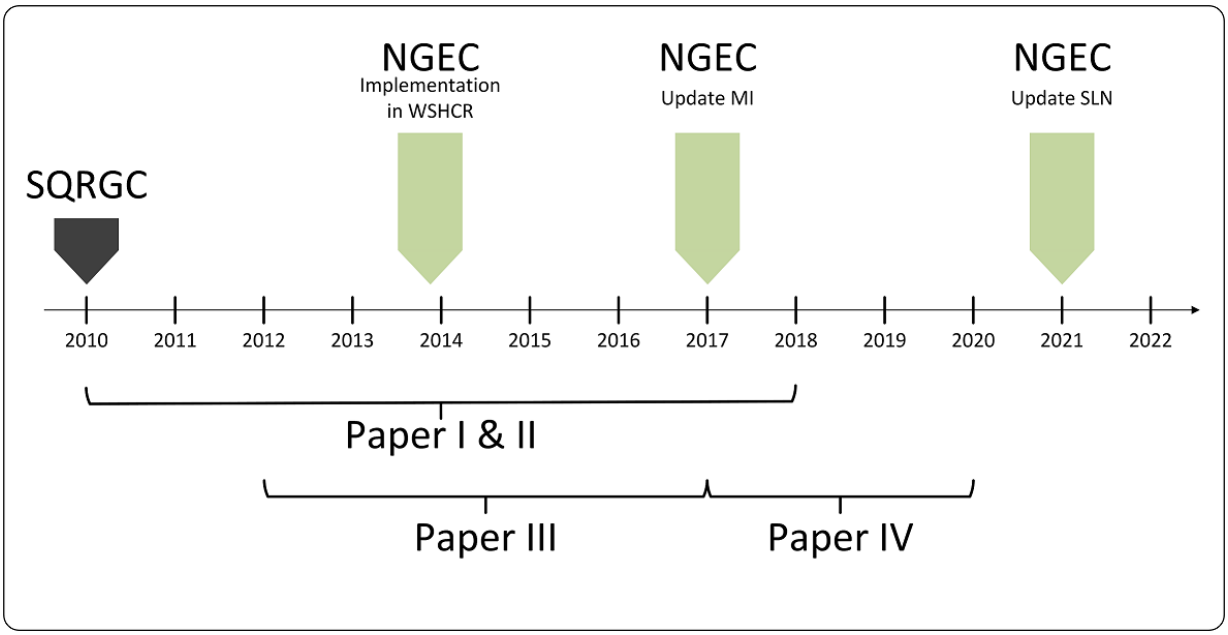

Figure 8. *Timeline of the thesis Papers and guidelines*

Abbreviations: SQRGC= Swedish Quality Register of Gynecological Cancer, NGEC= National Guidelines for Endometrial Cancer, WSHCR= Western Sweden Health Care Region, MI= Myometrial Infiltration, SLN= Sentinel Lymph Node

Although there was a shift in treatment guidelines for risk stratification and surgery, the recommended adjuvant treatment regimens were basically unchanged during the time period for all the studies. The recommended chemotherapy protocol consisted of four cycles of paclitaxel and carboplatin. The radiotherapy administered was (EBRT) to the pelvis, with extended paraaortic fields in the case of nodal metastases. VBT was administered in combination with EBRT or as single adjuvant treatment in the early study period.

Recommended surgical technique was MIS when possible. Robotic surgery for EC was introduced in January 2010 at SUH and was performed during the entire studied time period. The procedure of only hysterectomy and BSOE, without the lymphadenectomy, was more often performed as a laparoscopic assisted vaginal hysterectomy.

The staff of surgeons involved in EC care was to a large extent unchanged at all the sites during the studied time period. All pathology reports on EC in the WSHCR were reviewed by the reference gynecological pathologist team at SUH throughout the studied period.

Recurrence was verified with a biopsy when possible. In case of suspected or confirmed recurrence, a thoraco-abdominal CT was performed and further investigation with MRI and PET-CT if indicated. Patients who experienced relapse received treatment based on the extent of the recurrence and depended on the previous primary treatment. The guidelines stipulated surgical excision or radiotherapy for localized recurrences and chemotherapy or hormonal treatment for distant or disseminated recurrences.

The actual guidelines during the thesis study period are described below and there is an overview in *Table 6A and B* where a summary on the preoperative risk group classifications and treatment recommendations are presented.

2010 - November 2013
In the early study period, 2010 to November 2013 there were regional guidelines adopted in 2005. The preoperative classification was based on histology, p53 and flow cytometry in combination with a perioperative visual assessment of the MI being ≥ or <50%. The risk was determined as low, intermediate or high.

In the pre/perioperative low risk group, the recommended surgery was only hysterectomy and BSOE and in the intermediate risk group pelvic lymphadenectomy was added. For the high-risk group hysterectomy and BSOE was performed with the addition of omentectomy for the non-endometrioid EC. The rationale for no lymphadenectomy in the high-risk group was that all received adjuvant chemo- and radiotherapy regardless of lymph node status. At this time surgery was performed at the patients' home hospital, tertiary or county hospital, as pelvic lymphadenectomy was done at all the hospitals in the region.

December 2013 - 2017
In December 2013 the NGEC were implemented in the WSHCR and PPLND was introduced for the preoperative high-risk group. The preoperative risk group classification was a division of low or high risk depending on histology and the ploidy-status on flow cytometry. Non-endometrioid, high-grade endometrioid (FIGO grade 3) and non-diploid low-grade (FIGO grade 1-2) endometrioid EC

were considered high risk and diploid low-grade endometrioid EC was low risk. With the PPLND procedure in the high-risk group there was an adequate surgical staging. Postoperative treatment with adjuvant radiation was reserved to patients with lymph node metastases. Adjuvant chemotherapy was recommended to all non-endometrioid ECs. There was a centralization of the surgery for the high-risk patients to the tertiary center, SUH, when PPLND was added.

2017 - 2019

In 2017, the NGEC were revised regarding the risk group classifications of low-grade endometrioid EC and MI and/or CSI replaced the ploidy-status for the preoperative risk group allocation of low-grade endometrioid EC. The recommended methods for the assessment of MI and CSI, were TVUS or MRI. Non-endometrioid EC and high-grade endometrioid EC were still considered high-risk. The surgery in the high-risk group with PPLND in addition to hysterectomy and BSOE continued to be centralized to the tertiary center. Low-risk EC patients, with low-grade endometrioid EC and MI <50%, were recommended hysterectomy and BSOE, performed at the patients' home hospital. The assessment of MI and CSI for decision on referral to SUH was made at all the hospitals supported by the regional MDT. In the case of a faulty preoperative allocation to the low-risk group, that is if the postoperative pathology report showed high-risk features and only hysterectomy and BSOE had been performed, there was an indication for second surgery for restaging adding lymphadenectomy at the tertiary center.

Table 6A. Preoperative risk groups defined by treatment guidelines in the WSHCR

Preoperative risk group classification	**Regional guidelines** 2005-Nov 2013	**NGEC** Dec 2013-2016	**Revised NGEC** 2017-2019
Low risk	-EEC G1-2 diploid and p53 neg, MI<50%	-EEC G1-2, diploid	-EEC G1-2, MI <50%, no CSI
Intermediate risk	-EEC G1-2 with one risk factor; p53 pos or MI ≥50% or non-diploid -EEC G3, diploid, MI <50% -Cervical involvement	-	-
High risk	-EEC G1-2, non-diploid, MI ≥50% -EEC G3, diploid, MI ≥50% -EEC G3, non-diploid -NEC	-EEC G1-2, non-diploid -EEC G3 -NEC	-EEC G1-2, MI ≥50% or CSI -EEC G3 -NEC

Table 6B. Postoperative treatment in the WSHCR

Postoperative treatment	**Regional guidelines** 2005-Nov 2013	**NGEC** Dec 2013-2016	**Revised NGEC** 2017-2019
No treatment	Low risk*	-EEC G1-2, Stage I, diploid -EEC G1-2, Stage 1A, non-diploid -EEC G3, Stage IA, diploid	-EEC G1-3, Stage I -EEC G1-2, Stage II -EEC G3, Stage II, MI<50%
VBT	-Intermediate risk* G1-2 Stage 1A, non-diploid and no lymphadenectomy -Intermediate risk* with negative lymph nodes	-	-
VBT+EBRT	Intermediate risk* no lymphadenectomy	-	-
Chemotherapy		-EEC G3, Stage IB and IA, non-diploid -EEC G1-2, Stage IB, non-diploid -NEC Stage I	-NEC, Stage I-II -EEC G3, Stage II, MI≥50% -Stage IIIA
Chemotherapy+VBT		-Stage II	
Chemotherapy+VBT+ EBRT	High risk*	-Stage II, no lymphadenectomy -Stage IIIB	-Stage IIIB
Chemotherapy+EBRT		-All stage IIIC If no lymphadenectomy; -NEC -EEC G3 -G1-2, MI≥50%, with aneuploidy	-All stage IIIC If no lymphadenectomy; -NEC -EEC G3, MI≥50% -Stage II-IIIA

** Risk groups in table 6B corresponding to table 6A*
Abbreviations: EEC= endometrioid endometrial cancer, NEC= non-endometrioid endometrial cancer, G1= FIGO grade 1, G2= FIGO grade 2, G3= FIGO grade 3, MI= myometrial infiltration, CSI= cervical stroma invasion, NGEC= Swedish national guidelines for EC, WSHCR= Western Sweden Health Care Region, VBT= vaginal brachytherapy, EBRT= external beam radiotherapy

3.1.4 The PreOperative Diagnostics in low-grade Endometrial Cancer study

The regional process group for EC took the initiative to launch the PreOperative Diagnostics in low-grade Endometrial Cancer (PODEC) study in the context of the decision of the NGEC group to actually recommend TVUS performed by ultrasound gynecologists as the first-line alternative to MRI for the preoperative assessment of MI and CSI. There was a lack of specially trained ultrasound gynecologists, especially outside the main cities of Sweden and due to the

composition of the region and the workflow concerning the EC patients, it was difficult to see how this could be implemented. The hypothesis behind the PODEC study was to explore how TVUS in the hands of the gynecologists involved in the EC patients care would stand in comparison to MRI. The clinical decision on MI for the risk group allocation made during the PODEC study period was primarily based on the MRI result if there was a discrepancy between the methods. In addition, with the intention of avoiding second surgery for re-staging, uncertain cases were assessed as deep MI.

3.2 Study population

3.2.1 Study population Paper I & II

For Paper I-II, all patients with EC in the WSHCR and registered in the SQRGC 2010-2017 were reviewed (N=2237). Included in the studies were patients with preoperative early-stage EC, that is: no signs of extrauterine disease at preoperative work-up, and no evidence of disease (NED) at start of follow-up. Patients with preoperative advanced stages, FIGO stage IV and III, if revealed on preoperative imaging, was excluded from the study. In case of surgery after neoadjuvant treatment, palliative surgery or no surgery performed the patients were also excluded as well as patients with synchronous ovarian or other cancers. The endometrioid EC cohort was analyzed in Paper I and the non-endometrioid EC cohort was analyzed in Paper II.

The endometrioid cohort in Paper I included all grades of endometrioid EC and the variants referrable to endometrioid EC: endometrioid with squamous cell differentiation, endometrioid with villoglandular differentiation, endometrioid with secretory differentiation and mucinous. For Paper II, the non-endometrioid EC cohort included serous cancer, clear cell cancer, carcinosarcomas and a small number of undifferentiated epithelial tumors.

3.2.2 Study population Paper III

In Paper III, EC patients with preoperative early stage referred to SUH for primary surgery from 2012 to 2016 were included. Exclusions were made for patients with extrauterine disease on preoperative work-up, synchronous ovarian or other cancers and patients with surgery after neoadjuvant chemotherapy. Both low and high-risk EC from the Göteborg area were included and after the implementation of NGEC also the preoperative high-risk EC from the rest of the region. All patients who

underwent surgery were recommended thromboprophylaxis according to clinical guidelines, mostly four weeks of low-molecular heparin.

3.2.3 Study population Paper IV

For Paper IV, the PODEC study, the study population was recruited among patients with low-grade endometrioid EC and preoperative uterine confined tumor scheduled for primary surgery in the WSHCR. The inclusion period was from January 2017 to June 2019 at the county hospitals and from January 2017 to December 2019 at SUH.

Patients with superficial MI were considered low risk and the surgery was performed with only hysterectomy and BSOE at the patient´s home hospital. If the MI was judged deep or if CSI were suspected, the patient was allocated to the high-risk group and referred to Sahlgrenska hospital for surgery including PPLND in addition to hysterectomy and BSOE.

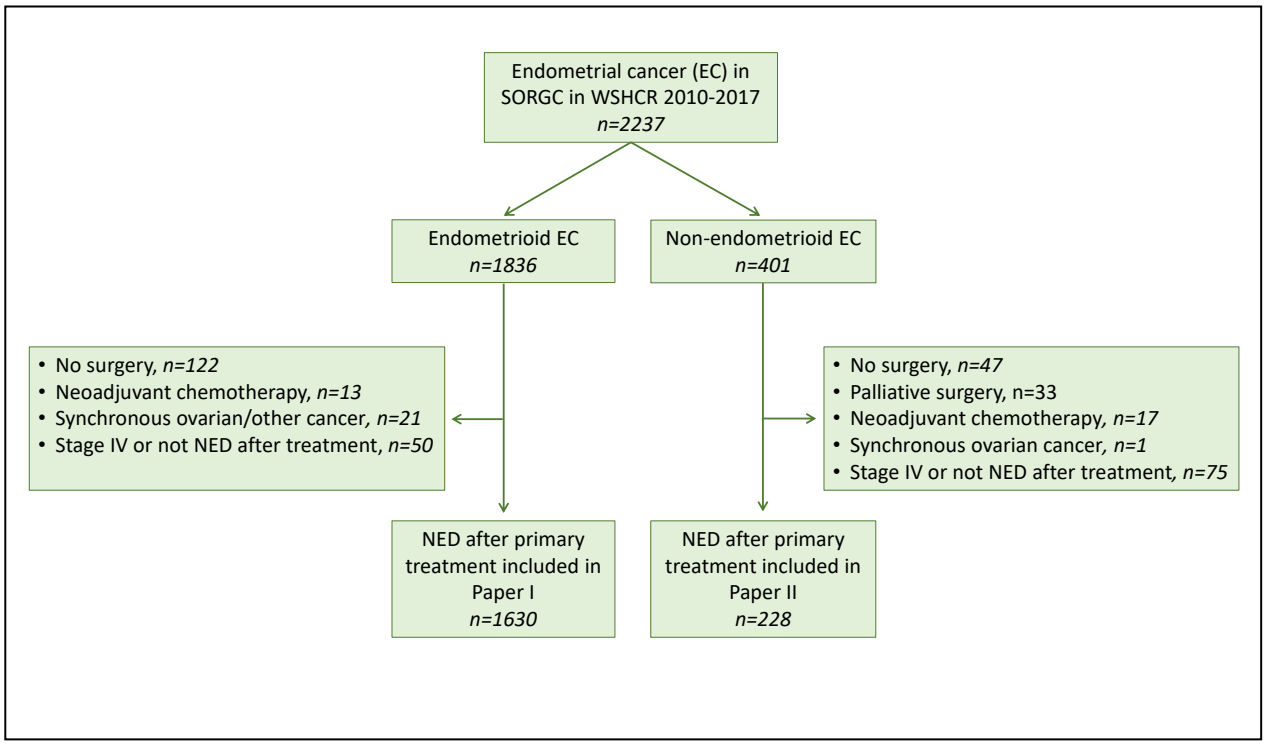

Figure 9. *Flowchart Paper I and II.*

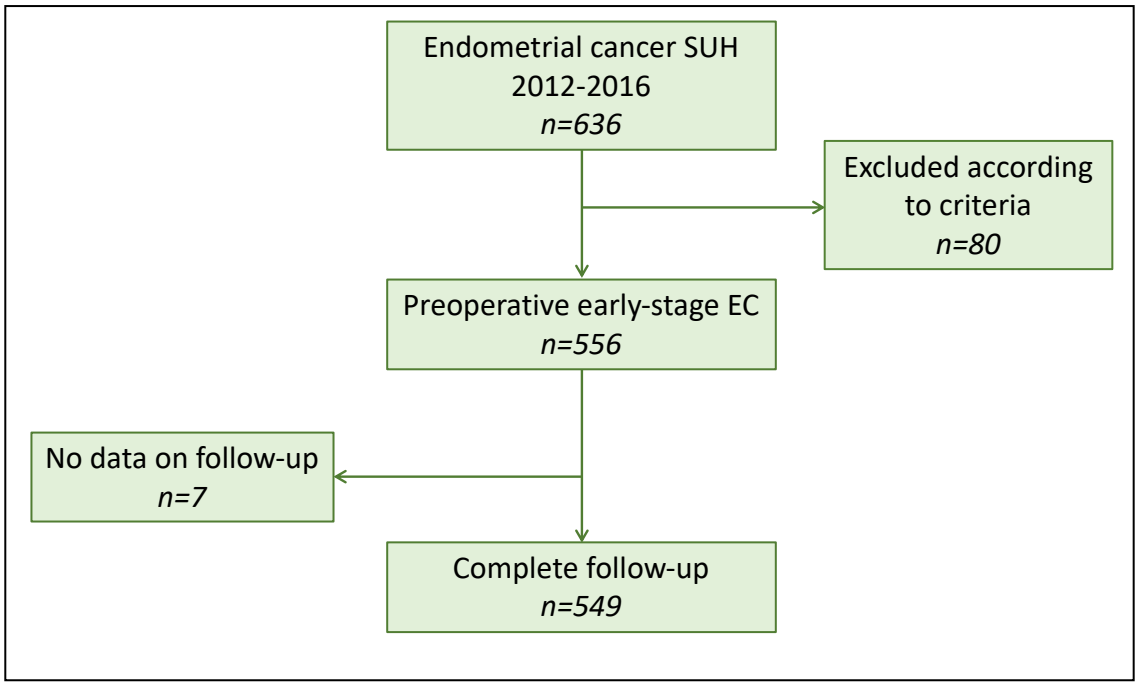

Figure 10. *Flowchart Paper III*

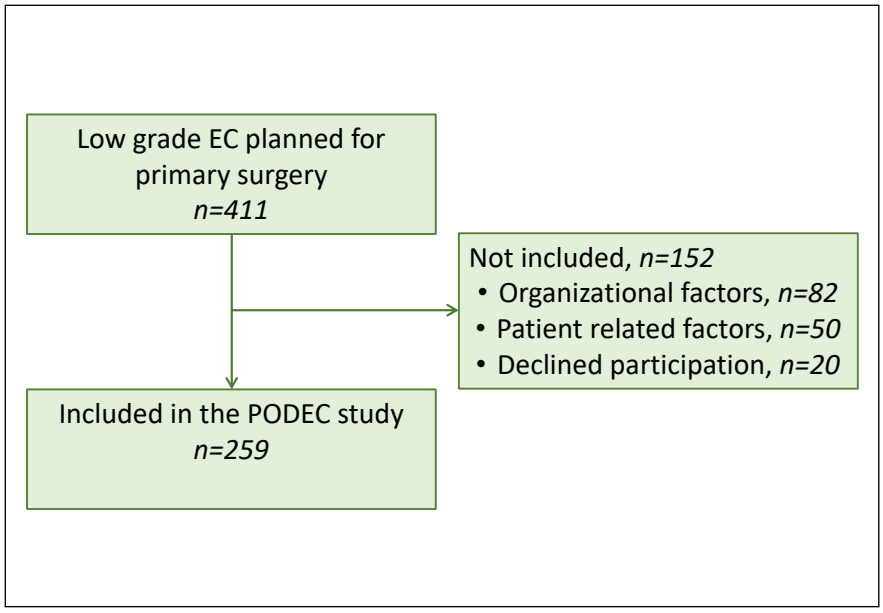

Figure 11. *Flowchart Paper IV (PODEC study)*

3.3 Data collection

3.3.1 Data collection Paper I&II

The SQRGC was used for extraction of data on variables concerning age, diagnosis date, primary surgery date, histology, grade, stage, surgical technique, adjuvant therapy and information on recurrences with date and localization of first

recurrence. The information in the SQRGC on the recurrences was considered incomplete. Data on recurrences had therefore to be confirmed and completed by reviewing medical records which were reviewed for all the patients by one reviewer, a subspecialist in gynecologic oncologic surgery (ÅÅ). The medical records´ review was performed during a defined and limited time period in order to be as adequate as possible; July through September 2020 and the vital status for all patients was retrieved from the SQRGC on 30 Sept 2020.

Recurrence date was set to the date of the biopsy or cytology confirming a recurrence. In some cases, there was no morphologic diagnosis of the recurrence and then the date of radiology leading to recurrence diagnosis was used.

The recurrences were described in relation to location and number of sites. For the analyses, recurrences were grouped as "only vaginal" and "all other" where "only vaginal" was defined as isolated vaginal recurrences as the vaginal recurrences in some cases had concurrent recurrences in other locations.

3.3.2 Data collection Paper III

Variables on age, diagnosis and surgery dates, mode and extent of surgery, adjuvant treatment, histology and grade of the tumor and surgical stage were retrieved from the SQRGC. There was some information in the register, although not extensive, on surgical complications as there was a regional registration also concerning complications.

The patients' medical records were reviewed to complete the study data base with information on BMI, ASA classification, comorbidities, previous surgery, smoking, length of stay, blood transfusions and blood loss, as these parameters were not in the register. Information on complications during the 30-day post-surgery period was scrutinized through all records available in the WSHCR including any indication of a postoperative complication on the following outpatient visits. In case of secondary surgery for staging, the mode of, and complications of, the first surgery were used in the study. The medical records were reviewed by two reviewers (ÅÅ and NW) during a three-month period in 2019 and vital status for the cohort was retrieved on 30 April 2019.

The criteria stipulated by the Martin *et al.*[136] were followed. The Martin criteria and the specifications of this study are displayed in *Table 7*.

For the analyses the patients were divided into age groups < or ≥75 years to investigate the effect on complications in the elderly cohort. In addition, we grouped BMI into < or ≥30, divided by the cutoff for obesity[129].

The patients' comorbidities were classified according to Charlson´s index[126-128]. The score 0-1 was considered low/normal and ≥2 as having a significant co-morbidity. Charlson´s index is presented in *Table 3*.

Complications within 30 days of surgery were categorized according to the Clavien-Dindo (CD) classification grading scale[138,184]. The patients were divided into two cohorts: CD 0-I if no or minor complications had occurred and CD II-V when clinically relevant complications had occurred. *Table 4* shows the CD classification.

Table 7. Martin criteria[136]

Criteria	**Requirement**	*Paper III*
Method of accruing data defined	Prospective or retrospective accrual of data are indicated	*Retrospective*
Duration of follow-up indicated	Report clarifies the time period of postoperative accrual of complications such as 30 days or same hospitalization	*30 days*
Outpatient information included	Study indicates that complications first identified following discharge are included in the analysis	*Yes*
Definitions of complications provided	Article defines at least one complication with specific inclusion criteria	*Yes*
Mortality rate and total complications indicated	The number of patients who died in the postoperative period of study are recorded together with cause of death	*Yes*
Morbidity rate and total complications indicated	The number of patients with any complication and the total number of complications are recorded	*Yes*
Procedure-specific complications included	Not defined for EC surgery in original paper/ but would be vaginal vault infections/hematoma or dehiscence, lymphatic leakage	*Yes*
Severity grade utilized	Any grading system designed to clarify severity of complications including "major and minor" is reported	*Yes, grading according to Clavien-Dindo*
Length-of-stay data	Median or mean length of stay indicated in the study	*Yes*
Risk factors included in the analysis	Evidence of risk stratification and method used indicated by study	*Yes, included in regression analyses*

3.3.3 Data collection Paper IV

The patients in the PODEC study were examined preoperatively with both TVUS and MRI to determine the depth of MI and CSI. A case report form (CRF) was used (*Appendix).* The TVUS was most often performed on the day of the preoperative

visit at SUH and in the county hospitals at a revisit to the gynecologist for diagnosis information and treatment planning. The MRI was done before or after the TVUS. The examinations were performed blinded to each other. The postoperative pathology report was used as a reference of the MI and CSI.

Deep MI was defined as infiltration ≥50% of the myometrium. The antero-posterior (AP) measures of the uterus and the tumor as well as the sagittal and transverse length of the tumor was recorded in the CRF. Although the final assessment of deep MI was visual and subjective.

Transvaginal ultrasound

The TVUS were performed by the treating gynecologists at each of the participating hospitals. All gynecologists were previously well acquainted with the use of TVUS as this is a part of a routine gynecology exam. A short introduction in the methodology of ultrasound assessment in EC, especially MI and CSI, was arranged for the group of gynecologists during half a day with an expert in gynecological ultrasound. Additionally, there was an offer of one or two days of field studies with the expert. The assessment was based on the International Endometrial Tumor Analysis group (IETA) guidelines[185]. The performance of the ultrasound machines was at minimum level corresponding to Voluson E6, but most of the examinations were performed with Voluson E10. Doppler was allowed and encouraged but no ultrasound contrast enhancement substance was used.

Magnetic Resonance Imaging

The MRI was conducted according to the European Society of Urogenital Radiology (ESUR) guidelines protocol for EC[186], adapted for this study as specified in Paper IV. All cases were reviewed at SUH by two radiologists. One of them was a senior radiologist experienced in gynecological MRI (last author of Paper IV) but without prior experience with this specific assessment and the other a radiologist with limited previous experience in gynecological MRI (joint first author of Paper IV). The performance of the MRI machines was 3T in all hospitals but one where it was 1.5T. At all sites, multiparametric MRI including contrast medium enhancement and diffusion weighted imaging was performed.

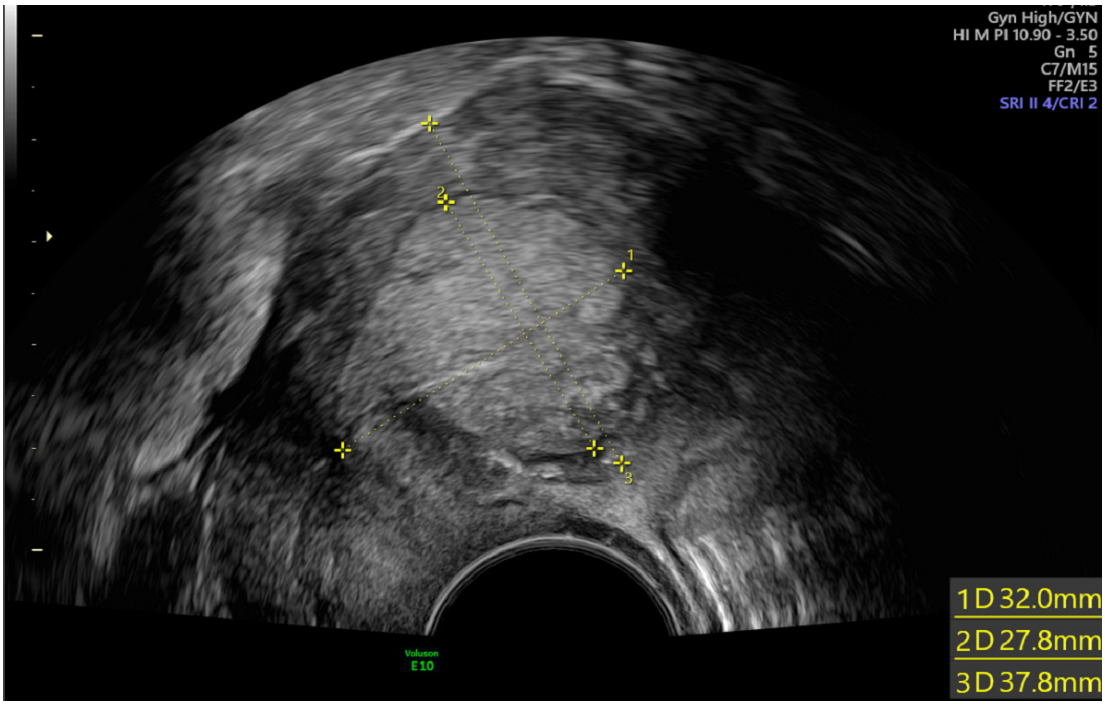

Figure 12A

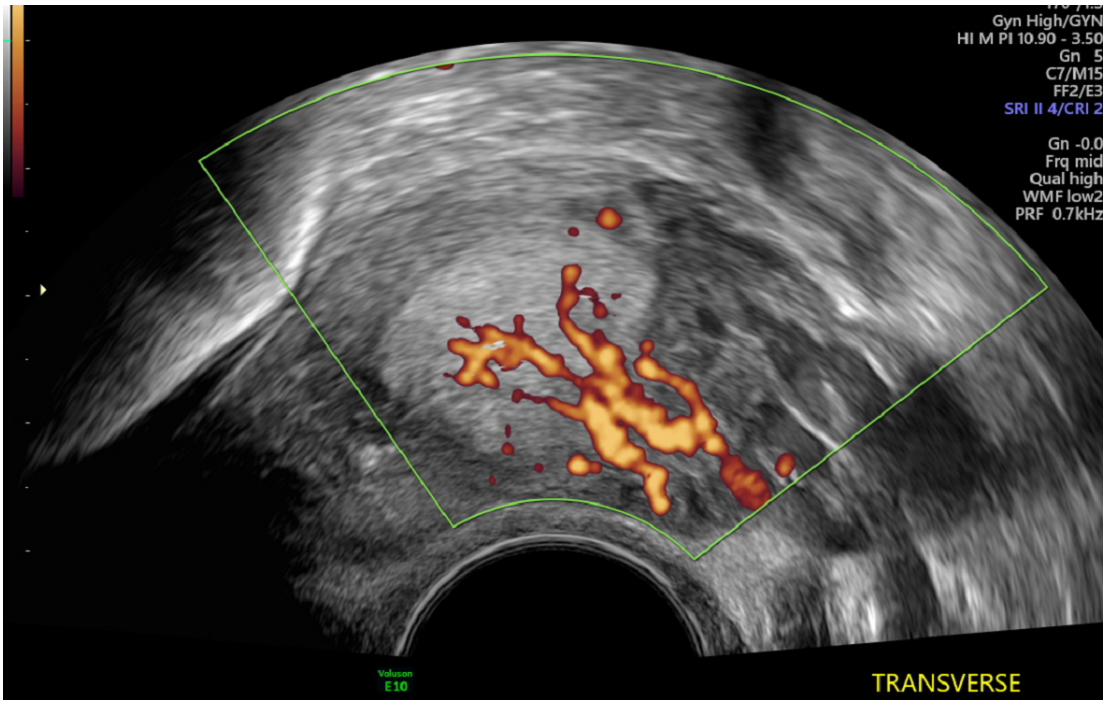

Figure 12B

Figure 12. *Example of Transvaginal ultrasound (TVUS) in the PODEC study. Patient with FIGO grade 1 endometrioid endometrial cancer, assessed as deep myometrial infiltration.* ***A*** *) anteroposterior and sagittal measurements* ***B)*** *doppler*

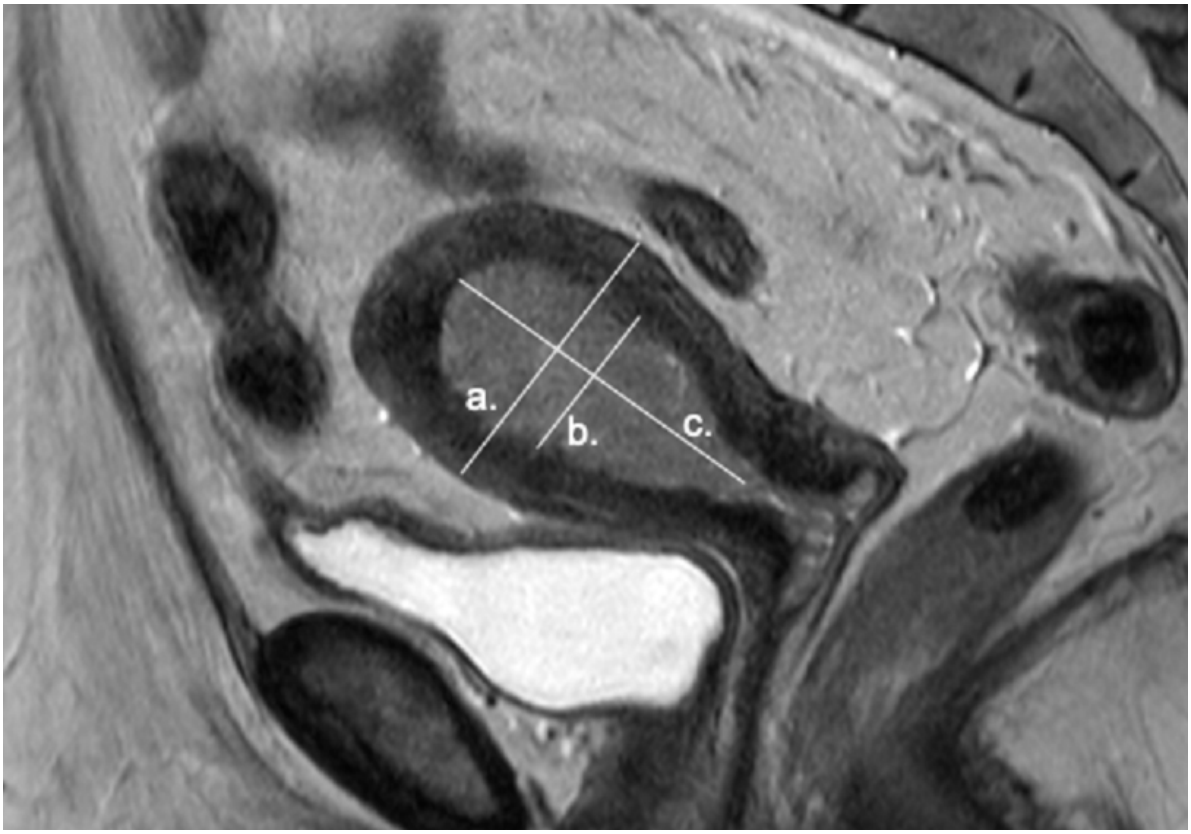

Figure 13. *Example of MRI in the PODEC study, T2-weighted sequence. Patient with FIGO grade 2 endometrioid endometrial cancer, assessed as deep myometrial infiltration. Lines a, b and c corresponding to the measurements in the case report form (CRF).*

3.4 Statistical analyses

In this thesis a variation of descriptive statistics, statistical tests, survival analyses and regression analyses have been used to match the data sets in the studies, described in more detail below. In Paper I, II & III a professional statistician from RCC has assisted with the analyses and is co-author of the publications. In Paper IV the joint first author performed the statistic calculations in co-operation with a professional statistician. For all studies the level of significance was set to 5%, or a *p*-value of <0.05 for statistical significance with a two-sided test. The follow-up period for Paper I, II and III was truncated at five years, that is recurrences and survival for up to five years after diagnosis were included.

3.4.1 Statistical tests

Descriptive statistics with median and range was used for age in all papers and for time from diagnosis to recurrence in Paper I and II. The *Chi-squared test* was used for comparisons of categorial variables between the cohorts of recurrence or no

recurrence in Paper I and II and for the cohort of no complication (CD 0-I) and complication (CD II-V) in Paper III. When the cell counts were less than five, *Fisher´s exact test* was used for the comparisons. For the continuous variables in Paper I, II, III, Shapiro Wilks and graphical examination were used to determine the distribution of the data. The *Student´s t-test* was used for normal distribution and the *Mann Whitney U* test for non-normal distribution. The *Log rank test* was used in Paper II and III to compare survival curves for determining statistically significant differences for survival. *Mc Nemar´s* test was used in Paper IV to compare the performance of TVUS versus MRI for the detection of deep MI and CSI. For the agreement between TVUS and MRI Cohen´s kappa was also performed. *Cohen´s kappa and Mc Nemar´s test* was further used to test the inter-reader agreement between the two different MRI readers.

3.4.2 Survival analyses

Overall survival (OS) was calculated with the Kaplan-Meier method[187] in Paper I, II and III. All patients in the cohort with the disease and all deaths disregarding the cause of death are included in the OS.

Net survival (NS) was calculated in Paper I with the Pohar Perme method[188,189] in which death rates of the Swedish population were used for the estimation. This is a *relative survival (RS)* measure where other causes of death are taken into account.

Disease-free survival (DFS) was estimated with the Kaplan-Meier method in Paper I and II.

Competing risk analysis was performed in Paper I in which the cumulative incidence function (CIF)[190] was used for the probability of having a recurrence while taking into account the competing event death without recurrence.

3.4.3 Regression analyses

In Paper I *the Fine and Gray proportional sub distribution hazards´ regression model* was used in both a univariable and a multivariable regression analysis for studying the effect of potential risk factors for recurrence.

Cox proportional hazards regression was used in Paper II and III. In Paper II the hazard ratios (HR) for age, FIGO stage, primary treatment and surgery with lymphadenectomy as effects on DFS was calculated in uni- and multivariable analyses. In Paper III, a Cox proportional hazard multivariable regression with OS

as endpoint was performed with the variables FIGO stage, histology risk groups and complications.

A *uni- and multivariable binary logistic* regression was performed in Paper III for potential risk factors for complications.

3.4.4 Diagnostic accuracy

In Paper IV, sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) and accuracy on deep MI and CSI were calculated for TVUS and MRI.

3.5 Ethical approval and consideration

3.5.1 Paper I-III

For Paper I-III, The Regional Ethical review board in Gothenburg approved the studies with the decision in Dnr 871-17.

The patients were informed of the registration in the SQRGC and the individual's possibility to withdraw from the register, at the time of treatment. All patients were given the care prescribed by the guidelines present at the time of treatment and this was not affected by these studies. Following up the effects of given treatment and treatment guideline changes through registers such as the SQRGC are important for the future development of evidence-based guidelines for the benefit of patients. It can also be argued that it would not be ethical to keep patient data in registers if it was not used for adequate follow-up and research.

3.5.2 Paper IV

For paper IV The Regional Ethical review board in Gothenburg approved of the study with the decision in Dnr 527-16.

All patients consented to participation in the PODEC study. The study included one extra modality of preoperative assessment for the patients but with no alterations or delay in the treatment. The preoperative diagnostics were rather sharpened with the double assessments, a possible gain for the individual.

For all studies the data was handled unidentified throughout the analyses.

4. Results and comments

The results in this thesis will be presented according to outcome with an adjacent comment and related discussion. *Table 8* contains an overview of the patient and tumor characteristics for all papers.

Table 8. Patient and tumor characteristics Papers I-IV

	Paper I		Paper II		Paper III		Paper IV
Setting	WSHCR		WSHCR		SUH		WSHCR
Time period	2010-2017		2010-2017		2012-2016		2017-2019
Total number patients	1630		228		549		259
Study cohorts	**No recurrence**	**Recurrence**	**No recurrence**	**Recurrence**	**No compl. CD 0-I**	**Complication CD II-V**	
Cohort size	*n*=1494	*n*=136	*n*=161	*n*=67	*n*=441	*n*=108	
Age; median (range)	69 (31-94)	71 (47-90)	70 (41-89)	73 (51-88)	69 (35-93)	69 (31-90)	69 (38-89)
Histology and grade (endometrioid); *n* (%)							
Grade 1	640 (43.2)	25 (18.5)			146 (33.1)	23 (21.3)	153 (95.3)
Grade 2	674 (45.4)	86 (63.7)			166 (37.6)	40 (37.0)	79 (32.6)
Grade 3	163 (11.0)	24 (17.8)			56 (12.7)	19 (17.6)	10 (4.1)
Undefined/missing	6 (0.4)	0 (0.0)					
Mixed adenocarcinoma							4 (1.6)
Mucinous	11 (0.7)	1 (0.7)			2 (0.5)	1 (0.9)	
Serous			84 (52.2)	31 (46.3)	42 (9.5)	12 (11.1)	4 (1.6)
Clear cell			42 (26.1)	9 (13.4)	16 (3.6)	6 (5.6)	1 (0.4)
Carcinosarcoma			30 (18.6)	25 (37.3)	13 (2.9)	7 (6.5)	
Undifferentiated			5 (3.1)	2 (3.0)			1 (0.4)
FIGO stage; *n* (%)							
IA	1052 (70.4)	53 (39.0)	94 (58.4)	15 (22.4)	274 (62.1)	61 (56.5)	168 (64.9)
IB	260 (17.4)	37 (27.2)	19 (11.8)	14 (20.9)	75 (17.0)	17 (15.7)	45 (17.4)
II	85 (5.7)	14 (10.3)	17 (10.6)	13 (19.4)	42 (9.5)	6 (5.6)	20 (7.7)
IIIA	34 (2.3)	10 (7.4)	6 (3.7)	7 (10.4)	50 (11.3)	24 (22.2)	5 (1.9)
IIIB	26 (1.7)	11 (8.1)	6 (3.7)	5 (7.5)			6 (2.3)
IIIC	37 (2.5)	11 (8.1)	19 (11.8)	13 (19.4)			8 (3.1)
IVA							0 (0)
IVB							2 (0.8)
BMI; median (range)							28.8 (12.7-50.1)
BMI; n (%)							
<30					268 (60.8)	51 (47.2)	
≥30					173 (39.2)	56 (51.9)	
Missing					0 (0.0)	1 (0.9)	
Smoker; n (%)							
No					399 (90.5)	102 (94.4)	
Yes					39 (8.8)	6 (5.6)	
Missing					3 (0.7)	0 (0.0)	
Charlsons score; n (%)							
0-1					381 (86.4)	92 (85.2)	
≥2					60 (13.6)	16 (14.8)	

Cont.

Table 8 cont.

	Paper I		Paper II		Paper III		Paper IV
Study cohorts	**No recurrence**	**Recurrence**	**No recurrence**	**Recurrence**	**No compl. CD 0-I**	**Complication CD II-V**	
Surgical technique; *n* (%)							
Laparotomy	637 (42.6)	72 (52.9)	109 (67.7)	50 (74.6)	102 (23.1)	56 (51.9)	
Robotic assisted	575 (38.5)	46 (33.8)	45 (28.0)	15 (22.4)	309 (70.1)	50 (46.3)	
Laparoscopic and/or vaginal	282 (18.9)	18 (13.2)	7 (4.3)	2 (3.0)	30 (6.8)	2 (1.9)	
Primary treatment; *n* (%)							
Surgery alone	989 (66.2)	59 (43.4)			253 (57.4)	42 (38.9)	
Surgery + radiotherapy	253 (16.9)	25 (18.4)	5 (3.1)	7 (10.4)	188 (42.6)	66 (61.1)	
Surgery + chemotherapy	60 (4.0)	5 (3.7)	73 (45.3)	10 (14.9)			
Surgery + chemo- and radiotherapy	192 (12.9)	47 (34.6)	83 (51.6)	50 (74.6)			
Operating hospital; *n* (%)							
University hospital	689 (46.1)	72 (52.9)	106 (65.8)	41 (61.2)			
County hospital	799 (53.5)	64 (47.1)	55 (34.2)	26 (38.8)			
National guidelines implementation; *n* (%)							
Before	713 (47.7)	77 (56.6)	62 (38.5)	34 (50.7)	157 (35.6)	34 (31.5)	
After	781 (52.3)	59 (43.4)	99 (61.5)	33 (49.3)	284 (64.4)	74 (68.5)	
Pelvic lymph node dissection; *n* (%)							
Yes	357 (23.9)	39 (28.7)	95 (59.0)	25 (37.3)	145 (32.9)	62 (57.4)	
No	1137 (76.1)	97 (71.3)	66 (41.0)	42 (62.7)	296 (67.1)	46 (42.6)	
negative nodes					126 (86.9)	49 (79.0)	
positive nodes					19 (13.1)	13 (21.0)	
Paraaortic lymph node dissection; *n* (%)							
Yes	63 (4.2)	8 (5.9)	45 (28.0)	10 (14.9)	66 (15.0)	37 (34.3)	
No	1431 (95.8)	128 (94.1)	116 (72.0)	57 (85.1)	375 (85.0)	71 (65.7)	
Peritoneal washing; *n* (%)							
Negative	1301 (87.1)	107 (78.7)	12 (7.5)	14 (20.9)			
Positive	40 (2.7)	12 (8.8)	137 (85.1)	42 (62.7)			
Undefined/missing	153 (10.2)	17 (12.5)	12 (7.5)	11 (16.4)			
p53; *n* (%)							
Negative	605 (40.5)	61 (44.9)	20 (12.4)	6 (9.0)			
Positive	102 (6.8)	16 (11.8)	32 (19.9)	17 (25.4)			
Undefined/missing	787 (52.7)	59 (43.4)	109 (67.7)	44 (65.7)			
DNA flowcytometry; *n* (%)							
Diploidy	1017 (68.1)	78 (57.4)	38 (23.6)	9 (13.4)			
Non-diploidy	276 (18.5)	45 (33.1)	75 (46.6)	38 (56.7)			
Undefined/missing	201 (13.5)	13 (9.6)	48 (29.8)	20 (29.9)			
Follow-up in months; median (range)	60.0 (15.2-60.0)	60.0 (43.2-60.0)	60.0(33.3-60)	60.0(60.0-60)	53.1 (2.8-90.2)	49.9 (1.1-88.9)	

Abbreviations: WSHCR= Western Sweden Health Care Region, SUH= Sahlgrenska University Hospital, BMI= Body Mass Index, CD= Clavien Dindo

4.1 Study population

The study base for Papers I and II comprised 2237 patients diagnosed with EC, in the years 2010-2017, where 1836 (82%) were endometrioid and 401 (18%) non-endometrioid. After exclusion according to the defined criteria 1630 endometrioid EC and 228 non-endometrioid EC patients were included in the studies.

For Paper III 636 patients with EC were referred to SUH for surgery in the period 2012-2016 whereof 556 were included and 549 had complete data on complications and follow-up.

In Paper IV patients were included in the prospective multicenter PODEC study from January 2017 to June/December 2019. There were 411 potentially eligible patients with a preoperative diagnosis of low-grade EC. After missed inclusions and exclusions according to the defined criteria, 259 patients were included in the study. The flowcharts of the inclusion in all studies are found in *Figures 9-11*.

Comments

The distribution of endometrioid and non-endometrioid EC in Paper I and II corresponds approximately to what would be expected in a total cohort of EC based on previous reports. For example, Kilgore *et al.* reported 82.6% endometrioid and 17.4% non-endometrioid[192] and in GOG-201 81.7% endometrioid and 18.3% non-endometrioid EC was reported[30].

There was a shift towards higher stages after the introduction of NGEC due to the more accurate staging with lymphadenectomy in the high-risk group. Less adjuvant radiotherapy was administered where we in Paper II show a reduction to 42.4% in received adjuvant radiotherapy, alone or in combination with chemotherapy, compared to 92.7% in the early period, before NGEC, see *Table 9* for details. In Paper III the cohort after implementation of NGEC contained a larger portion of serous cancers. This was an effect of the referrals from the county hospitals for surgery with PPLND in the high-risk cases.

Table 9. Patient and tumor characteristics, before and after NGEC implementation

	Paper I		Paper II		Paper III	
	Before	**After**	**Before**	**After**	**Before**	**After**
Time period	2010-Nov 2013	Dec 2013-2017	2010-Nov 2013	Dec 2013-2017	2012-Nov 2013	Dec 2013-2016
Cohort size	*n*=790	*n*=840	*n*=96	*n*=132	*n*=193	*n*=363
Age			70.5 (41-88)	71 (49-89)	69 (45-92)	69 (31-93)
Pelvic lymph node dissection *n* (%)						
Yes	193 (24.4)	203 (24.2)	17 (17.7)	103 (78.0)	40 (20.7)	171 (47.1)
No	597 (75.6)	637 (75.8)	79 (82.3)	29 (22.0)	153 (79.3)	192 (52.9)
Paraaortic lymph node dissection *n* (%)						
Yes	5 (0.6)	66 (7.9)	1 (1.0)	54 (40.9)	3 (1.6)	101 (27.8)
No	785 (99.4)	774 (92.1)	95 (99.0)	78 (59.1)	190 (98.4)	262 (72.2)
FIGO stage						
IA			47 (49.0)	62 (47.0)	132 (68.4)	208 (57.3)
IB			12 (12.5)	21 (15.9)	27 (14.0)	65 (17.9)
II			13 (13.5)	17 (12.9)	16 (8.3)	32 (8.8)
III					18 (9.3)	58 (16.0)
IIIA			8 (8.3)	5 (3.8)		
IIIB			9 (9.4)	2 (1.5)		
IIIC			7 (7.3)	25 (18.9)		
Histology						
Endometrioid Grade 1					59 (30.6)	112 (30.9)
Endometrioid Grade 2					84 (43.5)	123 (33.9)
Endometrioid grade 3					27 (14.0)	49 (13.5)
Mucinous					0 (0.0)	3 (0.8)
Serous			41 (42.7)	74 (56.1)	9 (4.7)	46 (12.7)
Clearcell			23 (24.0)	28 (21.2)	8 (4.1)	14 (3.9)
Carcinosarcoma			29 (30.2)	26 (19.7)	6 (3.1)	16 (4.4)
Undifferentiated			3 (3.1)	4 (3.0)		
Complications CD grade						
No					147 (76.2)	259 (71.3)
Grade I					10 (5.2)	25 (6.9)
Grade II					25 (13.0)	54 (14.9)
Grade III					5 (2.6)	14 (3.9)
Grade IV					3 (1.6)	4 (1.1)
Grade V					1 (0.5)	2 (0.6)
Missing					2 (1.0)	5 (1.4)
Charlons score						
0-1					167 (86.5)	311 (85.7)
≥2					26 (13.5)	52 (14.3)
Operating hospital						
University			46 (47.9)	101 (76.5)		
County			50 (52.1)	31 (23.5)		
Surgical technique						
Laparotomy			72 (75.0)	87 (65.9)	38 (19.7)	122 (33.6)
Robotic assisted			21 (21.9)	39 (29.5)	135 (69.9)	229 (63.1)
MIS other than robotic			3 (3.1)	6 (4.5)	20 (10.4)	12 (3.3)
Primary treatment *n* (%)						
Surgery alone					93 (48.2)	206 (56.7)
Surgery + radiotherapy			8 (8.3)	4 (3.0)	100 (51.8)	157 (43.3)
Surgery + chemotherapy			7 (7.3)	76 (57.6)		
Surgery + chemo- and radiotherapy			81 (84.4)	52 (39.4)		

Abbreviations: NGEC= National guidelines for Endometrial Cancer, CD= Clavien Dindo, MIS= minimalinvasive surgery

4.2 Recurrence

Results

- The recurrence rate was **8.3%** in the endometrioid EC cohort (Paper I) and **29.4%** in the non-endometrioid EC cohort (Paper II)
- Time to recurrence was a median of **22.5** months in endometrioid EC (Paper I) and **18.5** months in non-endometrioid EC (Paper II)
- The most common site of recurrence was vaginal in endometrioid EC (Paper I) and abdominal in non-endometrioid EC (Paper II)
- For both the endometrioid and non-endometrioid EC cohorts in Paper I and II the patients with recurrence were on average older, had higher stage disease and more often positive peritoneal washings

Endometrioid EC (Paper I)
In the endometrioid EC cohort 136/1630 (8.3%) patients experienced a recurrence with a median time to first recurrence of 22.5 months (range 3.2-59.3). The recurrences were biopsy or cytology confirmed in 77.9% and there was one site of recurrence in 69.1%.

The localization of recurrence was "only vaginal" in 27.2%. As many as 32.4% of the recurrences were at a distant location, that is in parenchymatous organs, skeletal or most frequent in the lung. Recurrence sites are displayed in *Figure 14A.*

For the "only vaginal" recurrences the median time to recurrence was significantly shorter with a median of 17.8 months (range 3.2-58.3) (p=0.048), there were more diploid tumors (p=0.007), a tendency towards lower grade (p=0.071) and less adjuvant therapy (p=0.002) compared to "all other" recurrence sites.

The patients with a recurrence were older, had higher stage and higher-grade disease and more often positive peritoneal washings.

The cumulative incidence function (CIF) for risk of recurrence over five years with the competing event death was calculated and the cumulative incidence of recurrence for endometrioid EC at five years was 8.7% (95%CI:7.4-10.2), shown in *Figure 15.*

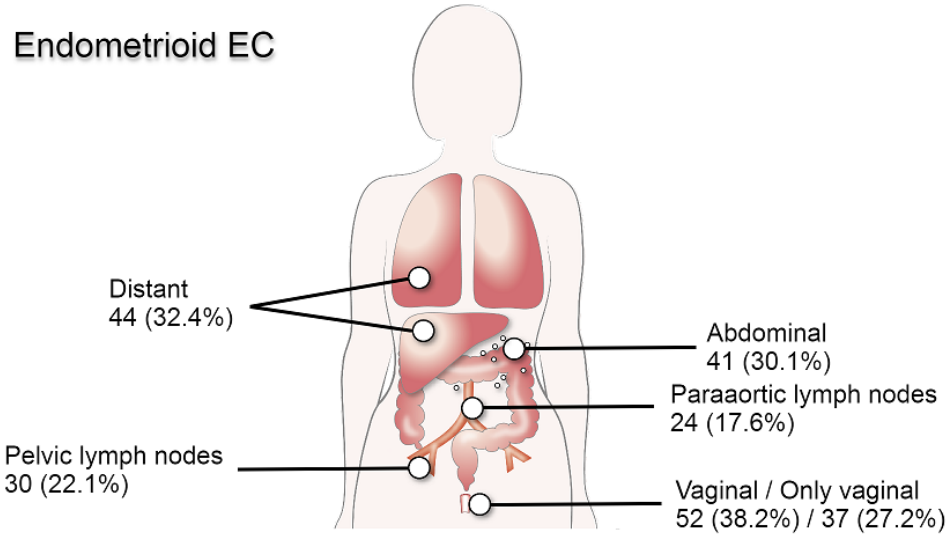

Figure 14A. *Recurrence localizations and frequencies in endometrioid endometrial cancer (Paper I). Illustration by Jan Funke*

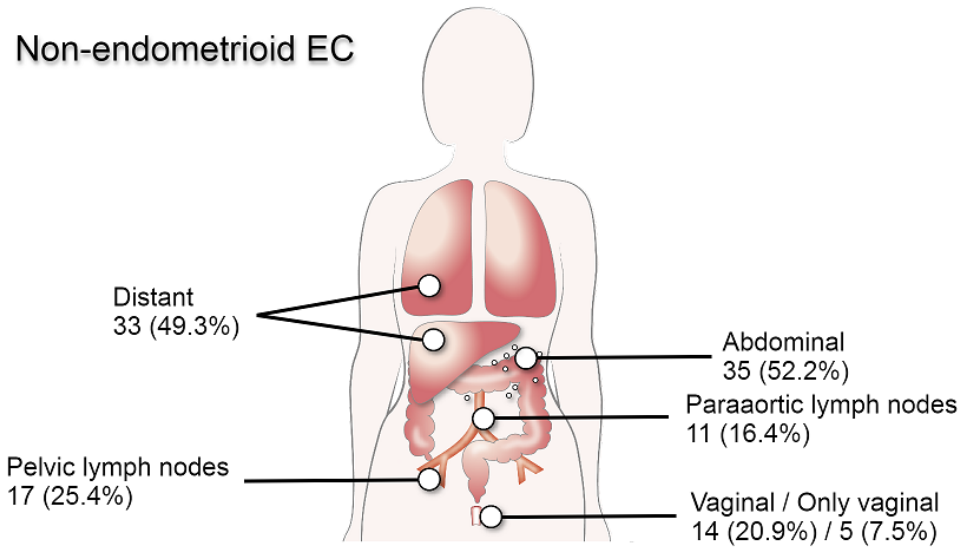

Figure 14B. *Recurrence localizations and frequencies in non-endometrioid endometrial cancer (Paper II). Illustration by Jan Funke*

Table 10. Recurrences Paper I and II

	Paper I Endometrioid *n=1630*	**Paper II Non-endometrioid** *n=228*
Recurrence within 5 years after diagnosis; *n*	136	67
Histology verified; *n* (%)		
Yes	106 (77.9)	48 (71.6)
No	30 (22.1)	19 (28.4)
Number of recurrence localisations; *n* (%)		
1	94 (69.1)	36 (53.7)
2	33 (24.3)	22 (32.8)
≥3	9 (6.6)	9 (13.4)
Time from diagnosis to recurrence (months); median	22.5 (3.2-59.3)	18.5 (6.1-54.9)

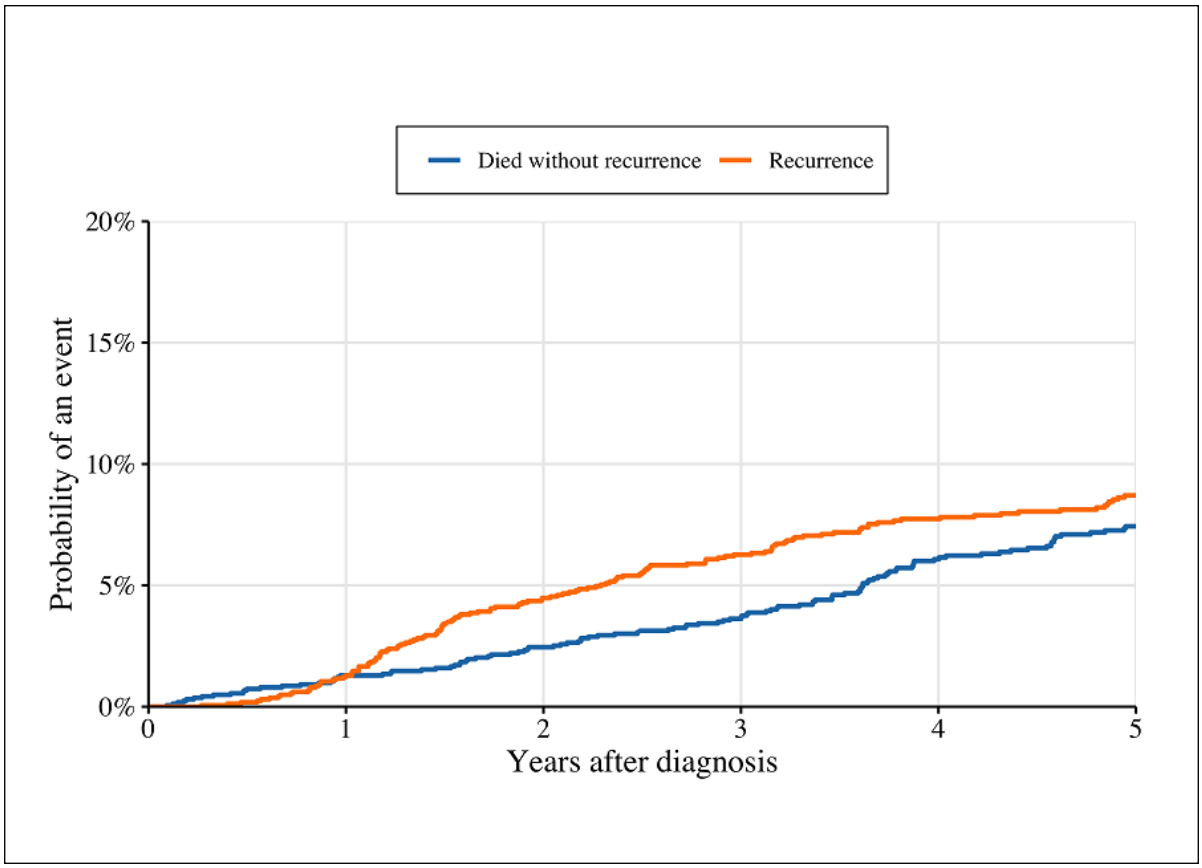

Figure 15. *Cumulative incidence frequency of recurrence in endometrioid endometrial cancer, with the competing event death.*

A regression analysis for the risk of recurrence was done with the Fine&Gray subdistribution hazards (SHR) model in which age, stage and primary treatment were found to be independent risk factors for recurrence in the multi-variable analysis, but not surgical technique or lymph node dissection. These results are displayed in *Figure 16.*

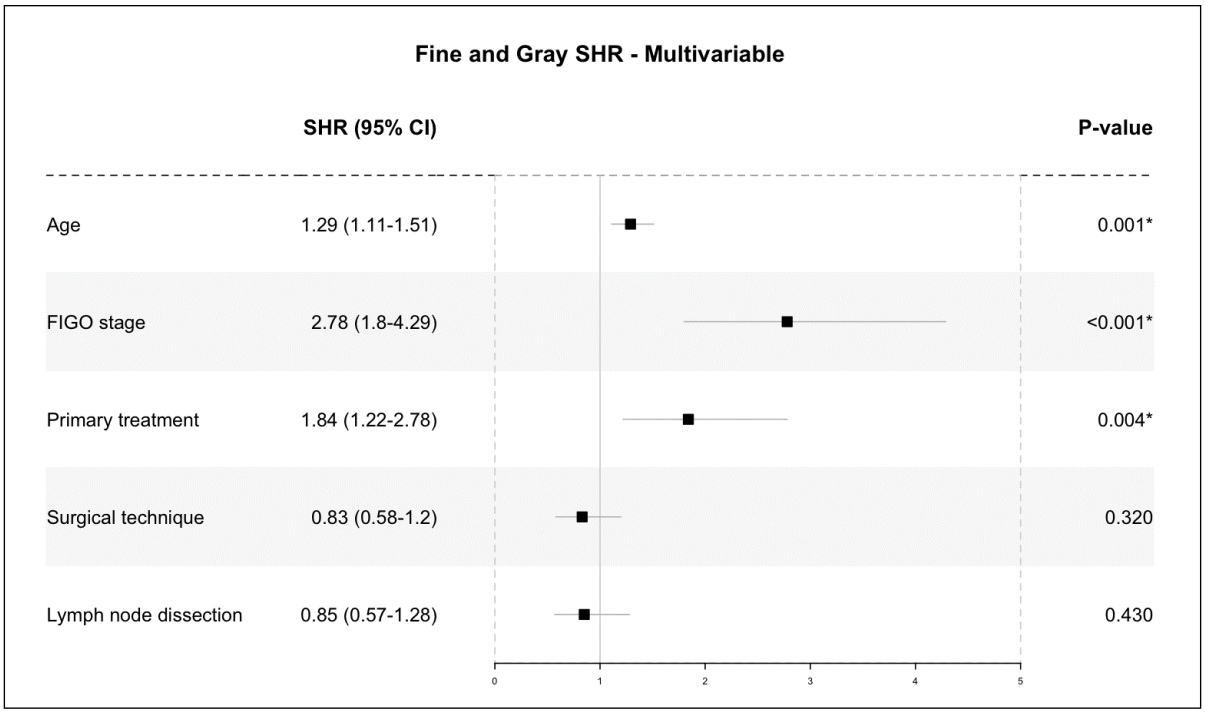

Figure 16. *Forest plot of the multivariable sub distribution hazards (SHR) for the risk of recurrence, with the variables age, stage, primary treatment, surgical technique and lymph node dissection (Paper I)*

Non-endometrioid EC (Paper II)

In the non-endometrioid EC cohort there were 67 (29.4%) patients with recurrences and the median time to first recurrence was 18.5 months (range 6.1-54.9). The recurrences were biopsy or cytology confirmed in 71.6% and there was one site of recurrence in 53.7%.

The “only vaginal” localization of recurrence was rare and only present in 7.5% of the non-endometrioid EC. Abdominal location including carcinomatosis was the most frequent site and constituted 52.2% of the recurrences. Recurrence sites are displayed in *Figure 14B.* Patients with recurrences were older, had higher stage disease than patients with no recurrence, and they had more often positive peritoneal washings. There were more often recurrences in carcinosarcoma or serous cancer than in clear cell cancer.

The cumulative incidence of recurrence at five years was for non-endometrioid EC 30.0% (95%CI:24.1-36.1). The CIF for risk of recurrence over five years with the competing event death is shown in *Figures 17A and B.*

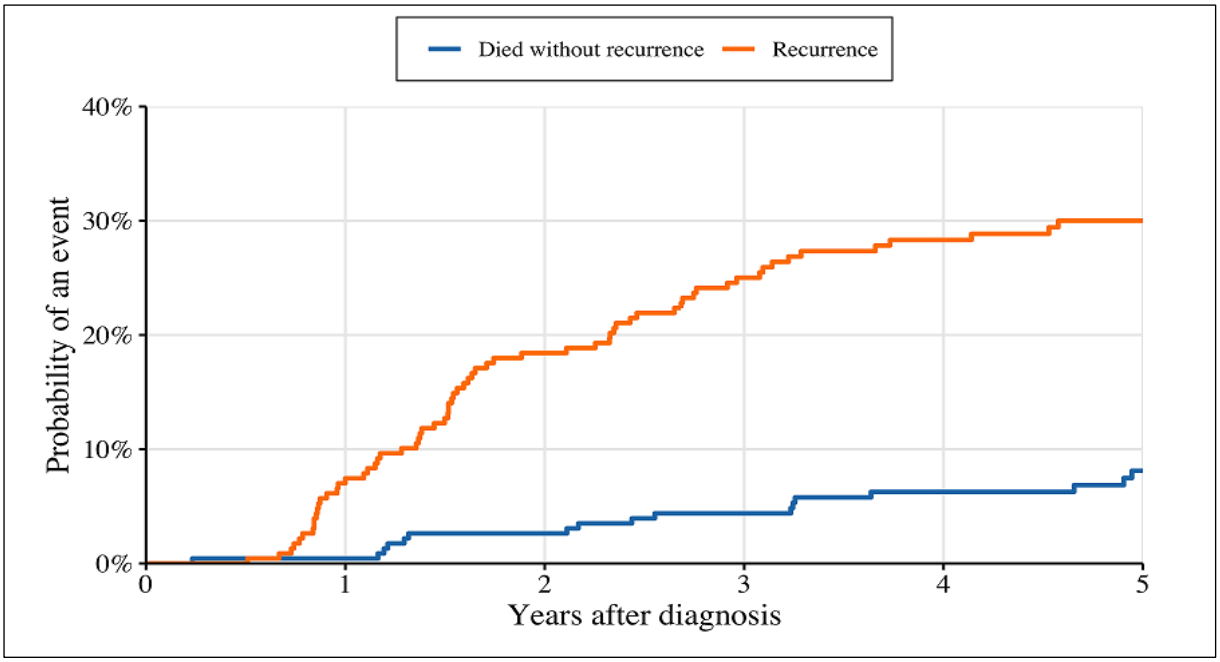

Figure 17A. *Cumulative incidence frequency (CIF) of recurrence in non-endometrioid endometrial cancer (EC), with the competing event death. Total cohort.*

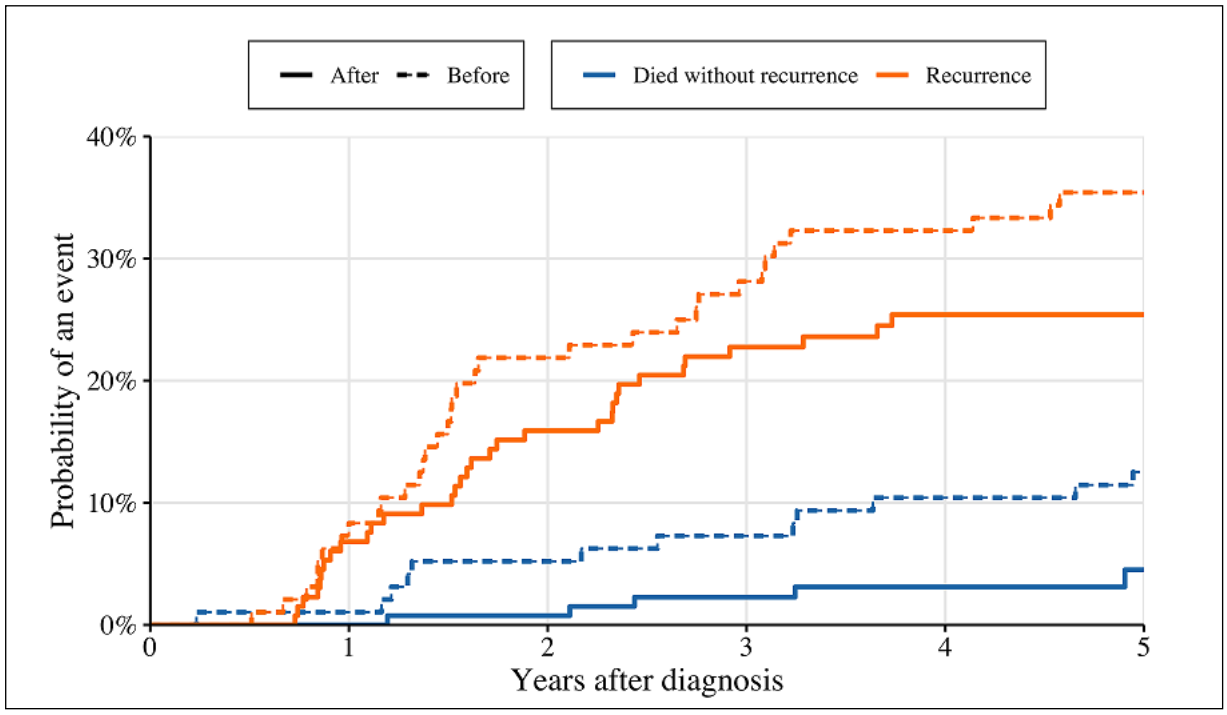

Figure 17B*. CIF of recurrence in non-endometrioid EC, with the competing event death. Cohorts before and after implementation of the national guidelines for EC (NGEC).*

Comments

The choice to only include patients with NED at start of follow-up was an attempt to show a truer risk of recurrence for an optimally treated patient with no known residual disease, rather than just progression of disease.

Below follows a discussion of our results on recurrences in Paper I and II in the light of findings of others although it is difficult to make direct comparisons as the case mixes and follow-up time vary between studies. *Table 11* displays a summary of some studies on recurrences in EC.

The recurrence rate was higher in the non-endometrioid than in the endometrioid EC cohort, like findings by others[84,159]. The recurrence rates are somewhat difficult to compare between studies due to different selection of cohorts. Fujimoto *et al.* presented a cohort of endometrioid EC, similar in composition to our cohort in Paper I, and reported a recurrence rate of 9.3%. Esselen *et al.* also presented a cohort of only endometrioid early stage with surgery as primary treatment and reported a 7.2% recurrence rate[193]. Nwachukwu *et al.* recently published cohort of 222 endometrioid FIGO grade 1 FIGO stage IA[96] and found a recurrence rate of 7.65%. For the non-endometrioid EC cohort it is hard to find comparable cohorts in the literature as the non-endometrioid ECs often are analyzed together with high-grade endometrioid EC as high-risk. However, in the PORTEC 3 study, featuring high-risk EC, a post-hoc analysis showed a recurrence rate of 28%[160].

Median time to recurrence was found to be somewhat shorter (4 months) in the non-endometrioid cohort than in the endometroid cohort as whole, but for endometrioid "only vaginal" recurrences time to recurrence was the shortest. This may be compared to the findings in a study by Vizza *et al.* who reported shorter time to recurrence in low-risk EC defined by the European ESMO-ESGO-ESTRO 2016 classification and longer time to recurrence in intermediate and intermediate-high risk groups[157].

Vaginal recurrence was the most common recurrence site in endometrioid EC. Notably, the portion of "only vaginal" localization of a recurrence was somewhat fewer (27%) than we may have expected compared to others, who have reported frequencies of 38-48% in early stage endometrioid EC of all grades[26,176]. These differences can be attributable to differences in case mixes and adjuvant treatment or how the recurrences are reported in regard to diagnostics and follow-up time.

The “Only vaginal” recurrence localization was more common in endometrioid EC than in non-endometrioid EC. Abdominal recurrence, including carcinomatosis, was the most common site in non-endometrioid EC, indicating occult tumor spread in the peritoneal cavity similar to ovarian cancer. Notably, the second most common recurrence manifestation in endometrioid EC is not abdominal but distant, a route of spread of hematogenous character.

The difference in recurrence patterns of endometrioid and non-endometrioid EC indicate a difference in behavior based on tumor morphology where high grade endometrioid tumors seem to have more distant relapses than low-grade[26]. Non-endometrioid EC displays a more disseminated pattern of recurrence[84]. In a Danish nationwide study on 1166 patients, the low-intermediate risk had more locoregional recurrences and the high-risk group had more non-locoregional recurrences sites[149]. Similar findings were found in a German register study with nodal and distant recurrence being more predominant in the high-risk group and more local recurrences in the low risk[163]. Bendifallah *et al.* reported more nodal and distant recurrences in the high-risk group and the vaginal vault location or nodal the most common sites in the low to intermediate risk groups[159]. Gayar *et al.* investigated only endometrioid EC of early stage and found a relation between the tumor grade to recurrence localization with isolated vaginal recurrence being most common in FIGO grade 1 and distant most common in grade 3[26]. In the PORTEC-3 high-risk cohort a post hoc analysis on recurrence showed the most common type of relapse to be distant[160].

Tumor stage has an influence on the recurrence pattern. Fujimoto *et al.* showed in endometrioid EC more distant recurrences if lymph nodes were positive in contrast to a higher proportion of local recurrences if lymph nodes were negative in primary surgery[194]. Interestingly, Aloisi *et al.* did not find a high rate of isolated paraaortic recurrences in FIGO stage IIIC1 patients staged only with pelvic lymphaden-ectomy in the primary setting[64].

We did not find a significant difference between surgical methods for risk for recurrence in the multivariable analysis in Paper 1. There has been a fear of MIS causing more recurrences in EC, for instance as port site metastases. Several studies, including randomized, have not shown significantly more recurrences with laparoscopy compared to open surgery[192,195,196]. Although, some have found higher recurrence rates in subgroups. Concerns have been raised against MIS for extraction of very large uterus in high-risk EC, with a proposed increased risk of

abdominal recurrences, which was shown in a Canadian retrospective study[197]. We did not have data on uterine size in our study and were therefore unable to perform such an analysis. Furthermore, Song *et al.* published a study with an increased risk of recurrence after robotic surgery in intermediate risk endometrioid EC who had received postoperative radiotherapy[198]. A continued follow-up of surgical technique in relation to recurrence in larger studies is needed.

In Paper I, two contingency tables are presented as an overview of the risk of recurrence in relation to tumor grade and stage. In the table only including patients who underwent lymphadenectomy, the risk of recurrence appeared to be higher (10.2%) than in the table of the total cohort. When interpreting these results, it is important to consider that in the lymphadenectomy cohort there was some preoperative risk factor in all patients who had lymphadenectomy, ie: suspected deep MI, non-diploidy, grade 3 or suspected stage II.

Unfortunately, we did not have reliable data on LVSI, which would have been intriguing as this could have provided an explanation for some of the relapses in the endometrioid EC cohort. Many others have reported on LVSI as a prognostic factor and as one of the explanations for unexpected recurrences in low-grade endometrioid EC[86,89,91,92]. This may be further explored in coming studies utilizing populations-based register data for follow-up and recurrences.

Table 11. Overview of selected studies on recurrences in endometrial cancer

Author, year (study name)	Study design	Time period	Histology	Specifics	FIGO stage	Cohort size	Recurrence rate			
							Total (%)	Low risk (%)	Inter-mediate (%)	High risk (%)
Creutzberg, 2003 (PORTEC 1)	RCT	1990-1997	EEC	G1-2 MI ≥50%, G2-3 MI <50%		715	8.3			
Obermair, 2004	RSI	1993-2001	All	primary surgery		510	9.0			
Sanjuan, 2008	RSI	1997-2002	EEC	primary surgery		163	5.6			
Fujimoto, 2009	RSI	1993-2008	EEC		I-III	355	9.3			
Esselen, 2011	RSI	1994-2007	EEC	primary surgery		1061	7.2			
Walker, 2012 (LAP-2)	RCT	1996-2005	All	primary surgery		2616	11.4 /10.2**			
Weinberg, 2013	RSI	1996-2010	EEC	MI≥50%, G2-3, LVSI	I-II	336	17			
Kilgore, 2013	RSI	2005-2011	All	robotic surgery		499	8.4			
Ortoft, 2013	PRS	1998-1999	All	primary surgery		1166	16	6.3	22	32
Gayar, 2014	RSI	1988-2011	EEC		I-II	949	8			
Elshaikh, 2015	RSI	1990-2014	EEC		II	130	17.7			
Jeppesen, 2016	PRS	2005-2009	All		I-II	2612	7			
Bendifallah, 2017	RSI	2001-2012	All		I-III	829	21	9	9/16*	35
Han, 2017	RSI	1993-2013	EEC		I	521	5.8			
Ignatov, 2018	PRS	2000-2016	All		preop early	2177	11.6	6.0	16.0	20.7
Francis, 2019	RSI	2000-2016	All		I-II	2691	7.2			
Ortoft, 2019	PRS	2005-2012	EEC, NEC	MI ≥50% or G3	I	305	25.3			
de Boer, 2019 (PORTEC 3)	RCT	2006-2013	EEC, NEC	G3, MI ≥50% or LVSI	I-III	660	28			28
Vizza, 2020	RSI	2001-2013	All		I-III	758	19.5	9.6	16.7/17.1*	40.3
Ureyen, 2020	RSI	1993-2013	EEC	G1-2	IA	720	3.4			
Nwachukwu, 2021	RSI	1996-2017	EEC	G1	IA	222	7.65			
Åkesson, 2022	PRS	2010-2017	EEC	primary surgery	I-III	1630	8.3			
Åkesson, 2022	PRS	2010-2017	NEC	primary surgery	I-III	228	29			

Abbreviations: RCT= randomized control trial, RSI= retrospective single/multi institution study, PRS= population based register study, EEC= endometrioid endometrial cancer, NEC= non-endometrioid endometrial cancer, G= FIGO grade MI=myometrial infiltration, LVSI= lymph vascular space invasion
*=low intermediate/high intermediate
**=laparoscopy/laparotomy

4.3 Survival

Results

- In the endometrioid EC cohort the 5-year OS was **88.0%** and the NS **98.6%** (Paper I)
- In the non-endometrioid EC cohort the 5-year OS was **65.4%** and the NS **72.5%** (Paper II)
- The survival was very negatively affected in both endometrioid and non-endometrioid EC when recurrence occurred (Papers I and II)
- When the recurrence was "only vaginal" the survival was superior to "all other" recurrences (Paper I)
- A significant improvement in OS and DFS was found in non-endometrioid EC after the implementation of NGEC (Paper II)
- Survival in EC was affected by complications in the first 1.5 years after surgery (Paper III)

Overall survival

For endometrioid EC the 5-year OS for the total cohort was **88.0%** (95%CI:86.4-89.7) and for the total cohort non-endometrioid **65.4%** (95%CI:59.3-72.2). When a recurrence had occurred, the OS was **46.8%** (95%CI:38.8-56.4) in the endometrioid cohort and **13.4%** (95%CI:7.3-24.7) in the non-endometrioid cohort, compared to **91.9%** (95%CI:90.4-93.3) and **88.5%** (95%CI:83.4-93.9) when no recurrence occurred.

In Paper I the recurrences were divided in the groups; "only vaginal" and "all other" recurrences and for the "only vaginal" the OS was **77.0%** (95%CI:64.0-92.6) and for "all other" **36.1%** (95%CI:27.5-47.3).

For survival in relation to FIGO stages, the 5-year OS for FIGO stage I in endometrioid EC was **89.3%** (95%CI:87.7-91.1) and in non-endometrioid EC **77.5%** (95%CI:70.7-85.0). Furthermore, 5-year OS for FIGO stage II in endometrioid EC was **89.1%** (95%CI:82.9-95.8) compared to non-endometrioid EC **48.2%** (95%CI:32.2-70.8) and for FIGO stage III **73.1%** (95%CI:65.6-81.5) and **44.2%** (95%CI:32.5-60.0) respectively.

Regarding survival in relation to grade and histology the 5-year OS for endometrioid EC FIGO grade 1 was **94.5%** (95%CI:92.6-96.3), for FIGO grade 2 **84.9%** (95%CI:82.3–87.6) and for FIGO grade 3 **79.0%** (95%CI:73.1–85.3; Paper

I). In non-endometrioid EC the 5-year OS for carcinosarcoma was **49.6%** (95%CI:37.4-65.8), for serous carcinoma **66.5%** (95%CI:58.1-76.0) and for clear cell carcinoma **79.8%** (95%CI: 69.3-91.9; Paper II).

A comparison of the survival between the time periods before and after the implementation of NGEC was made for both the endometrioid and the non-endometrioid cohorts. For the non-endometrioid EC there was a significant improvement in OS after the implementation of NGEC with a 5-year OS **72.0%** (95%CI:64.2-80.7) compared to **57.3%** (95%CI:48.2-68.1) for the cohort before the NGEC (Log-rank *p*=0.018; Paper II). For the endometrioid EC cohort there was no statistically significant difference in survival between the time periods.

In Paper III the 5-year OS was analyzed with regard to complications where the 5-year OS was **83.0%** (95%CI:79.1-87.1) for no or minor complication (CD grade 0-I) and **74.3%** (95%CI:66.1-83.6) for complications (CD grade II-V).

In a Cox hazard regression model with OS as endpoint the variables stage, histology and complications were included. The variables for complication vs no complication was time-varying and violating the proportional hazards assumption why this was fitted in two time periods. In the multivariable regression displayed in *Figure 18* there was a significant lower OS for higher FIGO stage, high-risk histology and during the first 1.5 years for the group with complications CD grade II-V (Paper III).

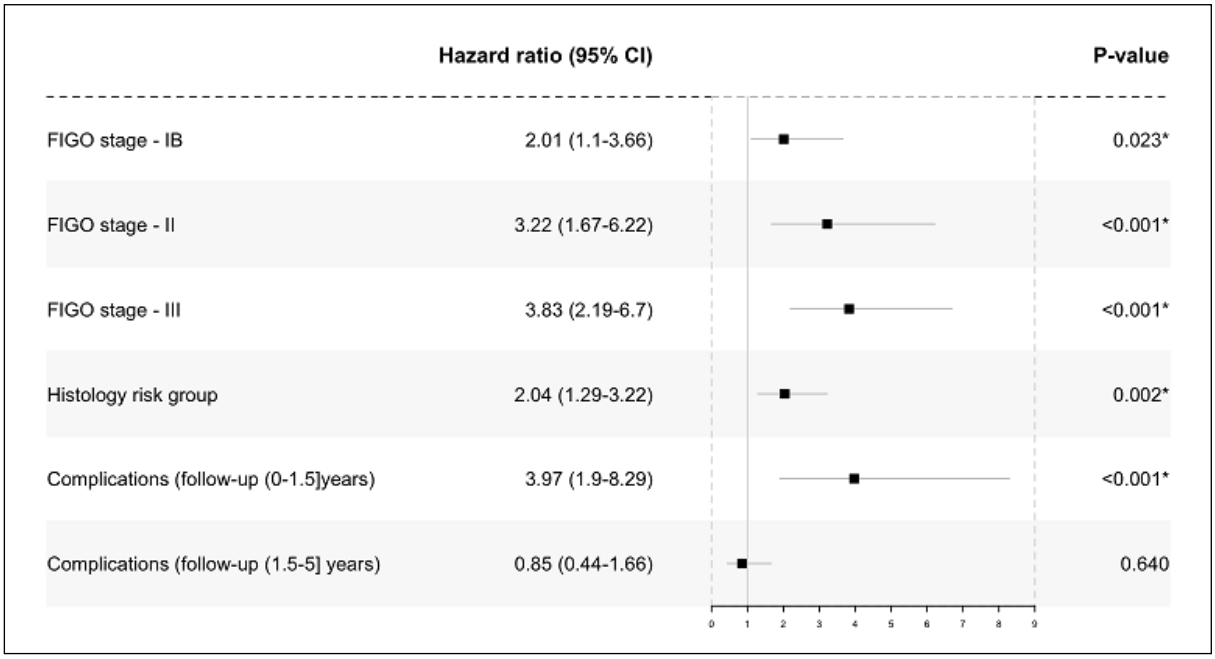

Figure 18. *Forest plot of multivariable Cox hazard regression model with overall survival (OS) as endpoint (Paper III)*

Net/relative survival

For both the endometrioid and non-endometrioid EC cohorts NS was analyzed. For the endometrioid EC cohort the NS is published alongside the OS in Paper I. The 5-year NS for endometrioid EC was **98.6%** (95%CI:96.5-100.7). Interestingly, for the endometrioid cohort without recurrence the NS was **102.8%** (95%CI:100.9-104.8) and **52.8%** (95%CI:43.7-63.6) if a recurrence occurred. For "only vaginal" recurrences the 5-year NS was **77.0%** (95% CI:64.0-92.6) for and for "all other" recurrences **36.1%** (95%CI:27.5-47.3).

For the non-endometrioid EC cohort the 5-year NS was **72.5%** (95%CI:65.5-80.2) For patients with a recurrence the 5-year NS was **14.5 %** (95%CI:7.9-26.8) and with no recurrence **98.1 %** (95%CI:92.1-104.5). The NS Kaplan-Meier curves for the non-endometrioid are displayed below in *Figures 19 A and B.*

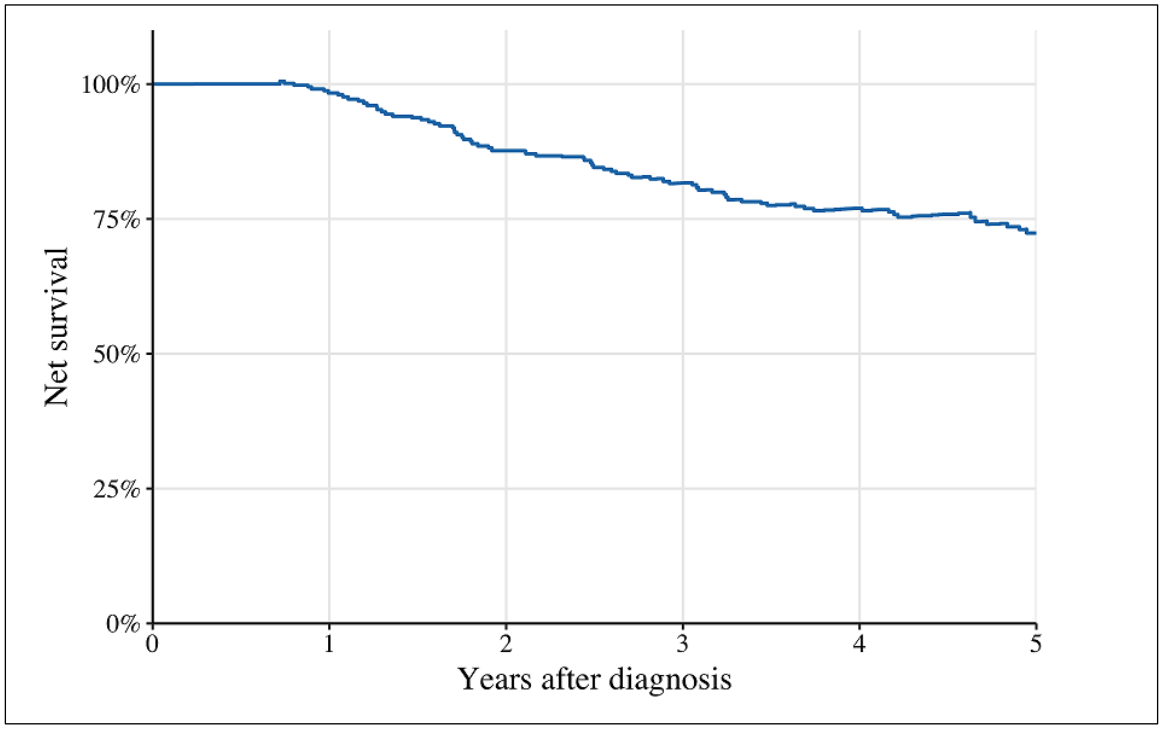

Figure 19A. *5-year Net survival (NS) for non-endometrioid endometrial cancer (EC), total cohort*

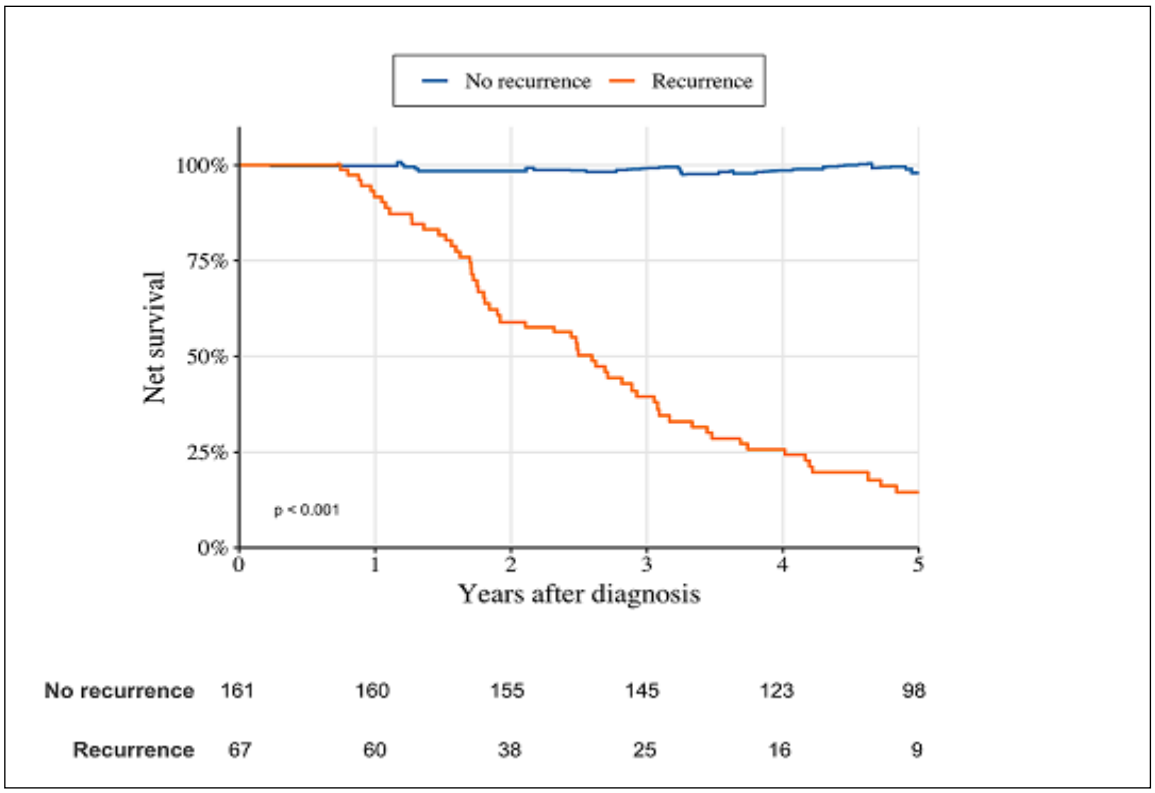

Figure 19B. *5-year NS for non-endometrioid EC, recurrence and no recurrence cohorts*

The 5-year NS Kaplan-Meier curves for both the endometrioid and the non-endometrioid cohorts before versus after implementation of the NGEC are displayed in *Figures 20A and B*. The 5-year NS for endometrioid EC before NGEC was **100.0%** (95%CI:97.4-102.6) and after **96.9%** (95%CI:93.5-100.4). For the non-endometrioid cohort the 5-year NS before NGEC was **61.8%** (95%CI:51.4-74.3) and after **81.4%** (95%CI:72.7-91.0; Log-rank p=0.012).

In Paper III the 5-year relative survival (RS) for the total cohort was **92.3%** (95%CI:88.1-96.8). Before the implementation of NGEC the 3-year RS was **97.7%** (95%CI:93.4-102.2) and after **93.9%** (95%CI:90.2-97.7) There was no statistically significant difference in 3-year RS (log-rank test, *p*= 0.195) shown in *Figure 21B*.

The 5-year RS for the groups CD grade 0-I and II-V is displayed in *Figure 22*.

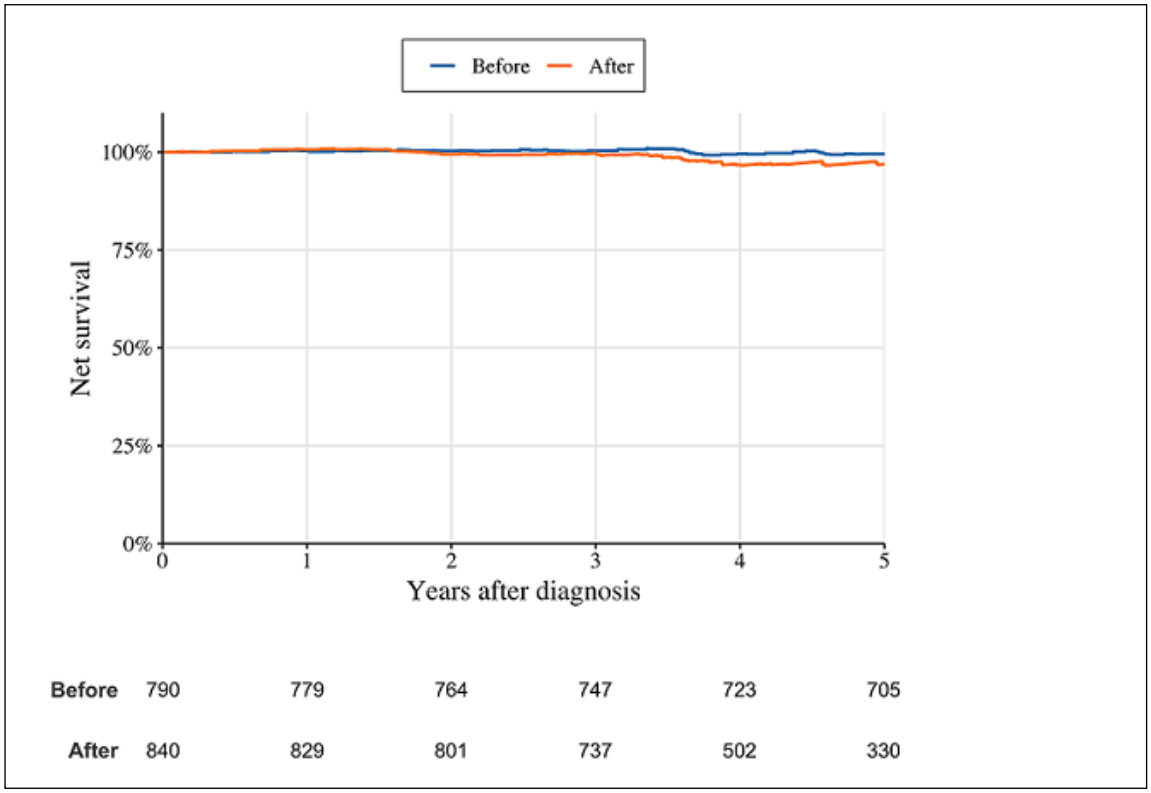

Figure 20A. *5-year Net survival (NS) for endometrioid EC before/after NGEC (Paper I)*

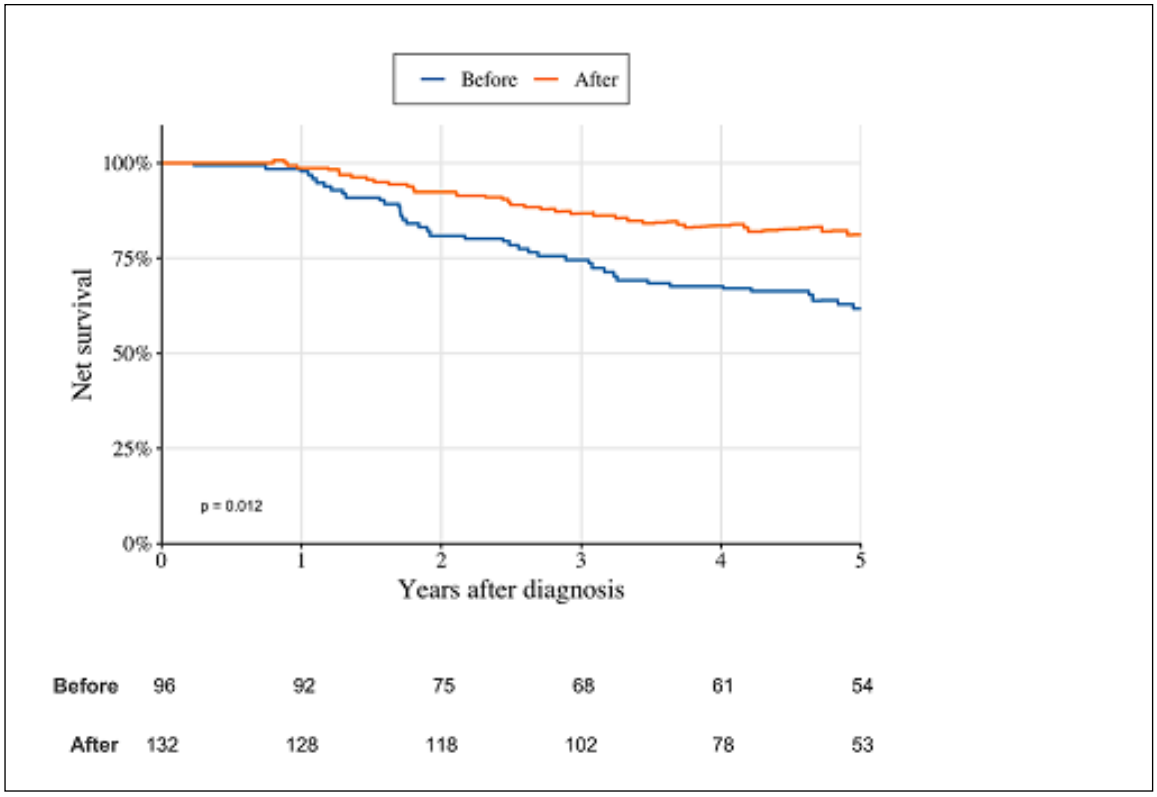

Figure 20B. *5-year NS for non-endometrioid EC before/after NGEC (Paper II)*

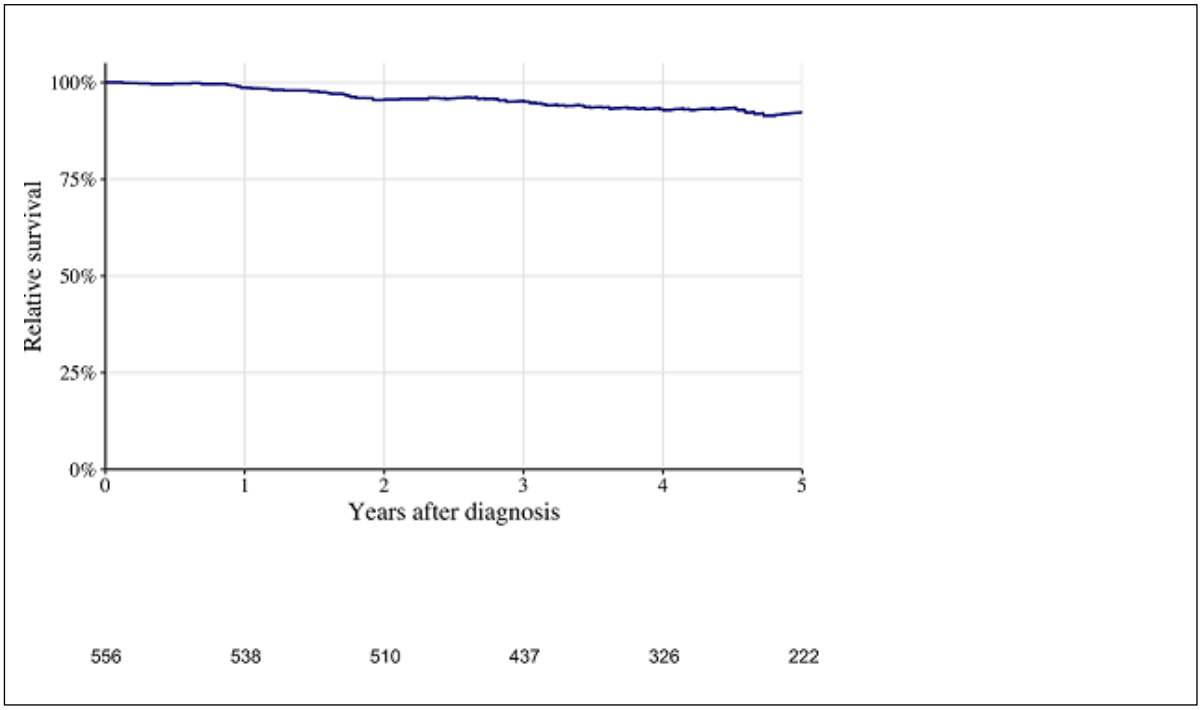

***Figure 21A**. 5-year Relative survival (RS) for the total cohort endometrial cancer (Paper III)*

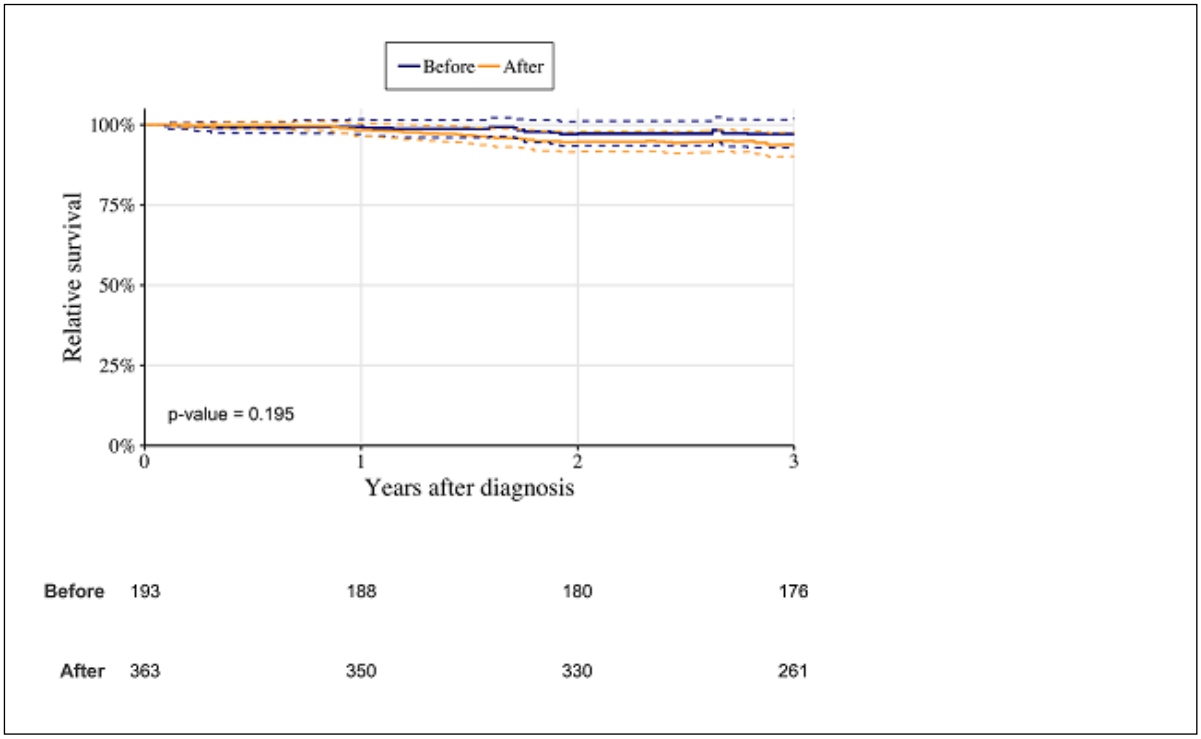

***Figure 21B.** 3-year RS for the cohorts before and after NGEC implementation (Paper III)*

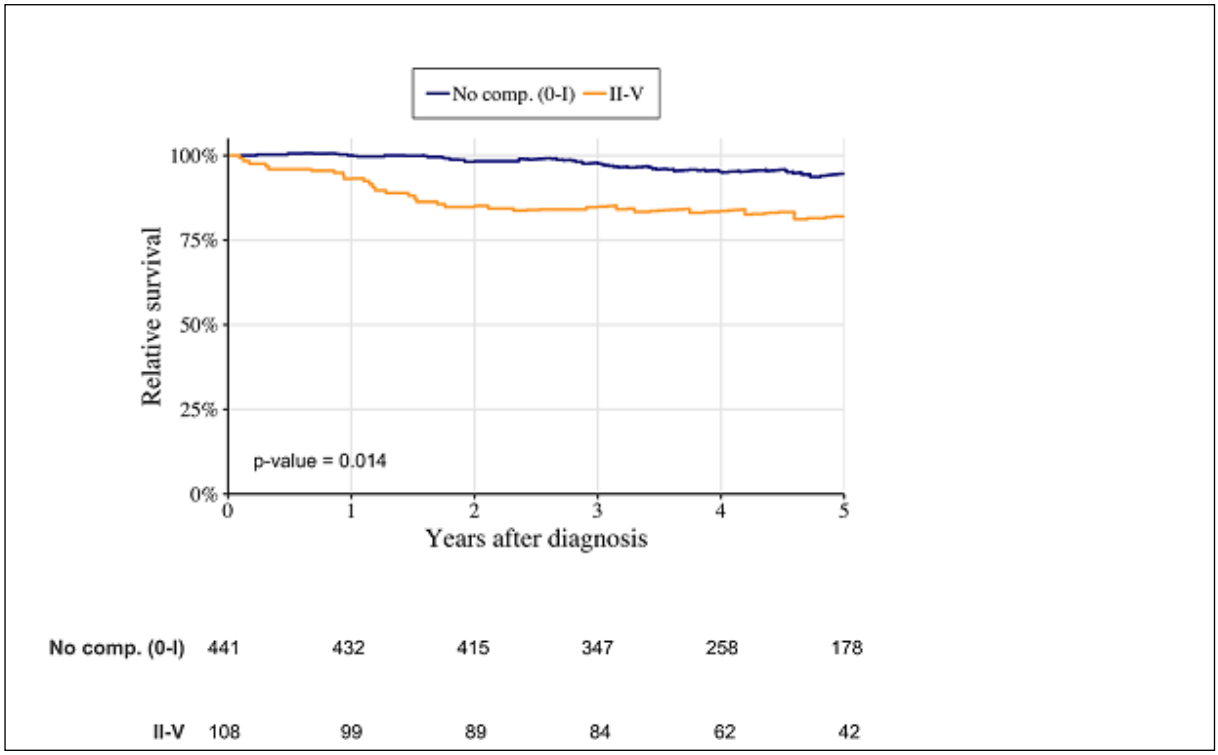

Figure 22. *5-year Relative survival for the cohort with no or minor complications;Clavien Dindo grade 0-I, and complications; Clavien Dindo grade II-IV (Paper III).*

Disease-free survival

The 5-year DFS for the endometrioid EC cohort was **83.9%** (95%CI:82.0-85.7; Paper I).

In the total non-endometrioid EC cohort, the 5-year DFS was **61.9%** (95%CI:55.7-68.7;Paper II). When dividing the non-endometrioid cohort in two, defined in time as before and after the implementation of NGEC we found an improved DFS in the later cohort.

This finding was analyzed in a Cox proportional hazards model with recurrence or death as endpoints with the variables age, FIGO stage, primary treatment, lymph node dissection and the time variable before or after the implementation of NGEC. In the multivariable regression age, FIGO stage and lymph node dissection were found to be statistically significant factors, displayed in *Figure 23.*

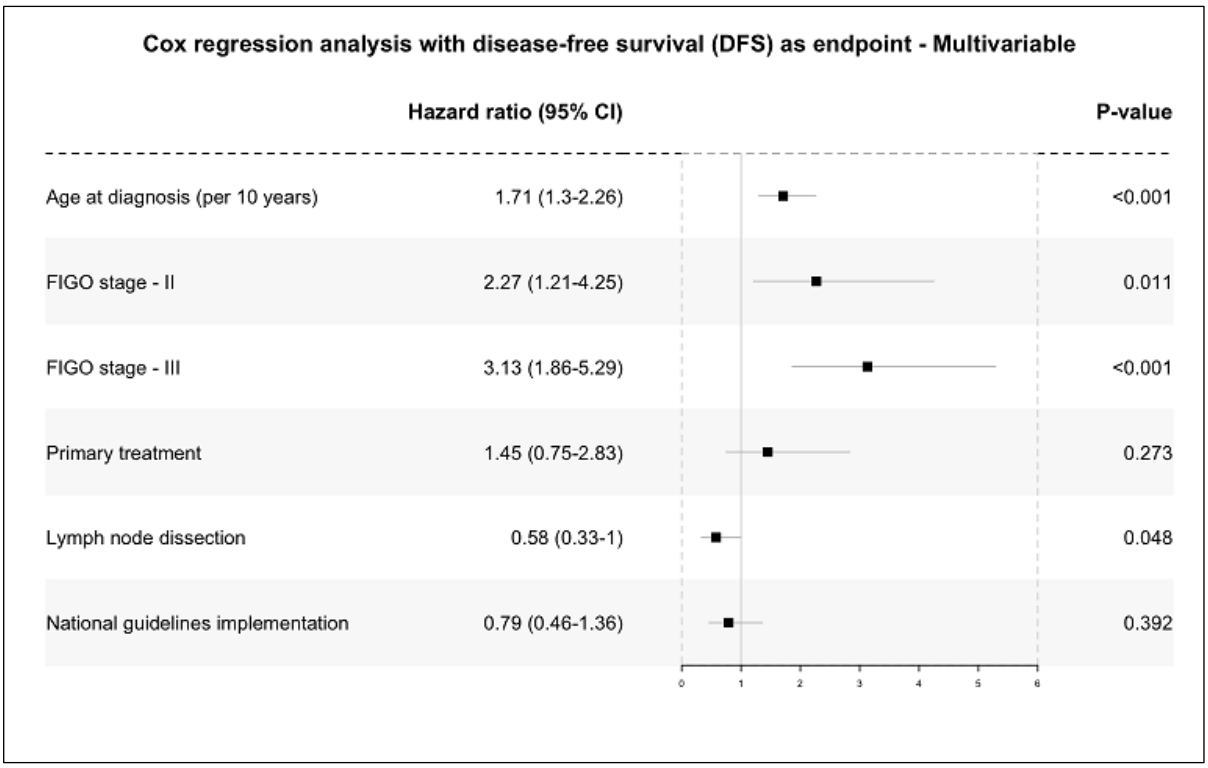

Figure 23. *Forest plot of multivariable Cox hazard regression with recurrence or death as endpoints (Paper II).*

Comments

Importantly, survival in our population-based studies was excellent both in the endometrioid and non-endometrioid cohorts when there was no diagnosed recurrence. Although, when a recurrence occurred, the survival was severely affected, except when the recurrence was an isolated vaginal. This is in line with previous findings[199]. In the randomized first PORTEC study the 3-year survival after vaginal relapse was 73%, in contrast to 8 and 14% after pelvic and distant relapse[144]. In a nationwide Danish population cohort register study, the 5-year OS was 64.8% when there was only a vaginal recurrence while 17.5% in distant recurrences[176]. Similar findings were reported by Francis *et al.*[200].

The prospect for cure is fairly good if recurrences are diagnosed in only one site, especially if the vagina is the only localization. If the primary treatment did not include pelvic radiation, this is often the first treatment choice in the recurrent setting, with good chances of cure. This is the argument for regular follow-up of the low-risk EC group, where adjuvant radiotherapy has not been given in the primary setting, to have the chance to catch a relapse as early as possible.

One of our findings is that non-endometrioid EC is associated with significantly worse survival than endometrioid EC in a population-based setting (Papers I and II). The inferior survival of non-endometrioid EC has also been reported by others[64,159]. For non-endometrioid EC, carcinosarcoma had the worst survival, followed by the serous type and best survival for clear cell cancer. This is in line with the results in the PORTEC 3 cohort, although there were no carcinosarcomas. Serous cancer had worse survival than clear cell and endometrioid grade 3 in that study[160].

In Paper III, we present data showing survival in EC appears to be affected in the first 1.5 years, if a surgical complication occurred. This finding we cannot fully explain but a theory may be that the complication affected the adjuvant treatment, either postponing or leading to a decision to refrain from adjuvant treatment.

Most interestingly, there was a statistically significant difference in survival between the cohorts before and after the implementation of NGEC in the non-endometrioid EC cohort of Paper II. This is in contrast to the findings for endometrioid EC in Paper I and the mixed cohort in Paper III, where no significant differences in survival were found. With the introduction of NGEC, PPLND was introduced in the high-risk group, including the non-endometrioid EC, for surgical staging and tailoring the adjuvant treatment. This change in recommendations entailed a large portion of the high-risk group going through PPLND at our tertiary center and less adjuvant radiotherapy was administered. So, several aspects of this change can be discussed in the light of these results: 1) Can there be a therapeutic effect of lymphadenectomy, at least in some subgroups such as non-endometrioid EC? 2) What is the relevance in this setting of the adjuvant treatment? 3) And what relevance did the centralization of surgery for high-risk EC entail?

For the first issue: We are not the first ones to imply a possible therapeutic effect of lymphadenectomy in EC. There have been some indications of this finding in subgroups of high-risk EC by other authors[57,59,60,201]. A Danish study showed an increased survival in high risk group after introducing lymphadenectomy compared to a historical cohort[202]. Although, in the large randomized trials this has not been proven[61,62] and the Cochrane report also conclude that lymphadenectomy is only for staging[63]. Thus, this is still an open question for the future and follow-up of the outcomes of the transition to sentinel node procedures for staging is advocated.

Regarding the second issue: adjuvant therapy, it is difficult to explain why less adjuvant radiotherapy would give improved survival in non-endometrioid EC. The answer could be that the adjuvant therapy was more individually customized and thereby gave the best effect. In comparison, when the adjuvant radiotherapy in stage I was omitted in Denmark the survival was not compromised[202].

When it comes to the third question concerning centralization of surgery, it has been shown in our center that centralization of surgery improved survival in ovarian cancer[203,204]. It may be proposed that the complex surgery of ovarian cancer can be much improved when performed by trained and experienced surgeons. For EC the surgery is not so complex but still there may be some gain as well.

4.4 Surgical complications

Results

- Surgical complications of higher grade are rare in EC surgery and the rate of complications CD grade ≥III was only **5.3%** (Paper III)
- Lymphadenectomy surgery for staging in EC is associated with an increased risk of clinically significant complications, of CD grade II or higher, with an Odds Ratio (OR) of **2.07** for pelvic lymphadenectomy and **2.63** for PPLND (Paper III)
- The risk of surgical complications of CD grade II or higher in the 30-day postoperative period was higher if lymphadenectomy was performed and lower with MIS (Paper III)
- A BMI of 30 or higher was associated with a higher risk of surgical complications. (Paper III)
- The risk of surgical complications of CD grade II or higher did not seem to be affected by the patients smoking habits, age or comorbidities (Paper III)

Surgical complications of any grade (CD I-V) in the 30-day postoperative period occurred in **26.0%** (143/549) of the patients in Paper III. Complications of CD grade II or higher were considered clinically significant and occurred in **19.7%** (108/549). Severe complications, CD grade ≥III, were few and affected only **5.3%** (29/549). The spectrum of complications in Paper III is described in *Table 12.*

For the analyses the cohort was divided into two groups: “no or minor complications” including complications of CD grade 0-I and “complications of clinical significance” including complications of CD grade II-V. The two groups were not different with regard to age, smoking or Charlson´s comorbidity score (Paper III).

The variables age, BMI, comorbidity score, surgical technique (open vs MIS/ robot), histology risk group and lymph node dissection were included in a binary logistic regression with surgical complications of CD grade ≥II as endpoint.

Table 12. Paper III complications descriptions and frequencies, graded according to the Clavien-Dindo classification[134], n=549. One patient could have more than one complication.

Grade	Definition	Paper III Complications and frequencies	
0	No complication		406
I	Any deviation from normal postoperative course (allowed: antiemetics, analgetics, diuretics, electrolytes, physiotherapy, superficial wound infection opened bedside)	Vaginal or wound lymphatic leakage	7
		Abdominal lymphfluid or lymphedema	6
		Nausea, constipation or prolonged pain	10
		Superficial wound infection	2
		Sensory nerve affection	2
		Hematoma or vaginal bleeding	3
		Other	5
II	Requiring pharmacological treatment, blood transfusion, parenteral nutrition	Blood transfusion	35
		Urinary tract infection	18
		Wound infection	10
		Vaginal vault or abdominal infection	20
		Pneumonia	6
		Venous thromboembolism	4
		Cardiac atrial fibrillation	1
		Constipation/paralytic ileus	7
III	Requiring surgical, endoscopic or radiological intervention		
IIIa	Not under general anesthesia	Vaginal vault abscess, drainage	6
		Residual urine, suprapubic catheter	1
IIIb	Under general anesthesia	Wound dehiscence, resutured	6
		Bowel obstraction, surgery	2
		Urinary tract injury, surgery	4
IV	Life-threatening complication		
IVa	Single organ dysfunction (incl. dialysis)	Pulmonary embolism, intensive care	2
		Pulmonary failure, intensive care	4
		Myocardial infarction	1
IVb	Multi organ dysfunction	Cardiac arrest, resuscitated	1
V	Death		2

In the multivariable regression analysis PPLND was found to be a risk factor with an OR of **2.63** (95%CI:1.32-5.31) for complications. High BMI ≥30 was also found to be a risk factor with an OR of **2.18** (95%CI:1.37-3.49). A reduced risk for complications was found for MIS/robotic surgery with an OR of **0.32** (95%CI: 0.18-0.56). The results of the multivariable regression analysis are found in the forest plot in *Figure 24.*

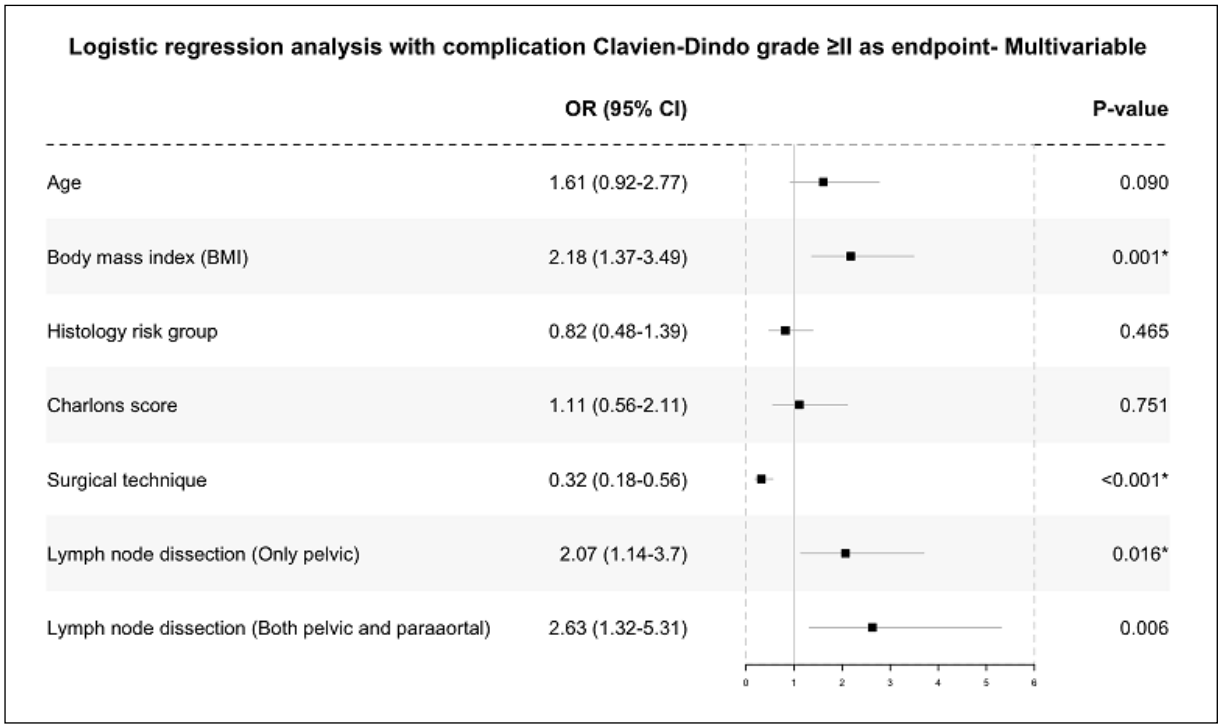

Figure 24. *Forest plot of multivariable binary logistic regression with surgical complications of Clavien Dindo grade ≥II as endpoint (Paper III).*

Comments

We chose to use the Clavien-Dindo grading system to standardize complications and severity, as it is widely used in surgical evaluation. The postoperative period of 30 days was included considering this would encompass most of the complications but not to be interfered with possible adjuvant treatment side effects. When studying surgical complications, the postoperative period of 30 days is often used. However, some complications may not show in the first 30 days. For example, there is a concern about vaginal dehiscence following hysterectomy, and the frequency is noted to be higher after robotic surgery than laparotomy, but the time from surgery to the event of dehiscence of the vaginal vault often appear later than the first 30 day period[205,206]. Another example is regarding thromboembolic events, which may become apparent later or around 1 month postoperatively[207]. A postoperative period of 60 or 90 days for studying complications has been proposed as more appropriate and may be considered in further studies.

Importantly, there was a low rate of severe complications, classified as CD grade ≥III the study. Complications were mostly at the CD grade I-II level, where we in this study made a cut-off at CD grade ≥2 as clinically significant since the CD

grade I complications did not require medical intervention and could have been underreported.

Comparing the complication rates between studies can be dubious due to different definitions, case-mixes and follow-up time. Our finding of a rate of severe complications CD grade ≥III of 5.3% is comparable to the rates found in a large Danish cohort of EC patients[208]. In that study the 90-day postoperative severe complications rate was reported to be 6.9% before and 5.7% after the introduction of robotic surgery for EC surgery in 2012.

After the study in Paper III was completed the reporting of complications for EC surgery has been incorporated into the national registration in SQRGC and since the year 2020 there is Swedish national data available. The nationally reported overall complication frequency for EC surgery was 11.8% for 2020 and 10.4% for 2021, based on 1014 and 789 reported surgical procedures[209]. The rates of complications CD grade ≥III or higher was 3.3% and 3.4%. When comparing these complications data to our study it must be noted that the reporting was not complete for all regions in Sweden. Although, in the WSHCR the reporting of surgical complications was high, and the frequencies of complications were comparable to the national reporting. The national complication rate in 2020-2021 seems to be lower than what we found in Paper III and may be attributed to the introduction of the sentinel node procedure in 2020, replacing the full pelvic and paraaortic lymphadenectomy.

The staging surgery in EC with lymphadenectomy renders complications. We found lymphadenectomy to be an independent risk factor for complications. This may further support the transition to surgical staging by sentinel lymph node procedure instead of lymphadenectomy. Polan *et al.* compared lymphadenectomy to no lymphadenectomy or sentinel lymph node procedure and found a significantly higher complication rate (3.6% of CD ≥3) in the lymphadenectomy group compared to both the no lymphadenectomy and sentinel node cohorts (2.0%)[210]. The advantages of the sentinel node procedure compared to full lymphadenectomy is supported by multiple studies[211-213] .

As obesity is a major concern among EC patients there has been an interest in surgical complications in relation to high BMI. The average BMI was high in our studies, as expected. Almost 42% of the patients in Paper III had BMI ≥30. Obesity was found to be an independent risk factor for complications as reported by

others[214,215]. Obesity may restrict the surgical possibility of complete staging. On the other hand, the high-risk disease is less prevalent in obese patients[215]. For the morbidly obese patients concerns have been raised towards respiratory complications due to the steep Trendelenburg position during robotic surgery, but this has not been the case. One study showed no more pulmonary complications in the patients with BMI >50 compared to BMI <50[216].

Complications in relation to surgical technique in EC have been studied by others and like us less complications with MIS compared to open surgery have been reported [217]. The advantage is greatest in the patients with a high BMI[133,215]. The added value of MIS/robotic surgery is the shorter time to recovery although long-term outcomes are similar. Robotic surgery and the evolvement of the sentinel lymph node concept have made the staging more feasible also in obese patients. In Denmark, a nationwide register study including more than 5000 patients following a centralization and broad introduction of robotic surgery for EC in 2012 found robotic surgery to be favorable in terms of a reduced rate of severe complications[208]. Moreover, Barrie *et al.* compared conventional laparoscopy to robotic assisted surgery and found no differences in the complications but a less frequent conversion rate and also fewer reported minor complications in robotic surgery [218].

Interestingly, we did not find a significant influence of a high Charlons score on surgical complications. Overall, the Charlons scores in the cohort were low. The major portion of the cohort, 86.2%, were categorized as Charlson´s score 0-1, which is comparable to the cohort in the recent Danish nationwide study[208]. In our study, there was a selection of patients when it came to the decision on the extent of surgery in relation to co-morbidities. Older patients and patients with multiple comorbidities did not undergo the full PPLND but only pelvic lymphadenectomy or in some cases surgery was limited to only hysterectomy and BSOE. This is obvious looking into the patient cohort who underwent full PPLND: they were younger (median age 65), had lower BMI (29% BMI >30) and a lower Charlsons´s score (96% Charlons score 0-1).

There was a low prevalence of smokers in the cohort, 8.2% which can be compared to 8-12% in the national statistics of smoking in Swedish women age 65-84 for the years 2012-2016[219]. There were not more smokers in the complications cohort compared to the no complication cohort.

4.5 Preoperative diagnostics with TVUS and MRI

Results

- The sensitivity of TVUS performed by gynecologists for the assessment of MI was 68% and the specificity was the same (Paper IV)
- For MRI the sensitivity for the assessment of MI was 73% and 70% respectively for the two readers and the specificity 88% and 80% (Paper IV)
- For the assessment of CSI, the sensitivity was much lower for both TVUS and MRI (32%, 40% and 46%) but the specificity was rather high (90%, 96% and 97%) (Paper IV)

The sensitivity, specificity, PPV, NPV and accuracy for the assessment of deep MI (≥50%) and CSI are displayed in *Table 13*.

Table 13. Accuracy of TVUS and MRI in the PODEC study

	TVUS % (95%CI)	**MRI Reader 1** % (95%CI)	**MRI Reader 2** % (95%CI)
MI ≥50%			
Sensitivity	68.2 (56.4-78.5)	73.1 (61.7-82.6)	70.1 (58.5-80.1)
Specificity	68.1 (61.2-74.4)	87.5 (82.3-91.6)	79.7 (73.6-84.9
PPV	42.5 (33.4-52.0)	67.1 (55.8-77.1)	54.7 (44.1-64.9)
NPV	86.1 (79.9-90.9)	90.3 (85.5-94.0)	88.4 (83.0-92.6)
Accuracy	68.1 (62.2-73.6)	83.8 (78.9-87.9)	77.2 (71.8-82.0)
CSI			
Sensitivity	32.3 (17.9-49.7)	40.6 (25.0-57.8)	46.9 (30.5-63.8)
Specificity	90.2 (85.8-93.6)	96.0 (92.9-98.0)	96.9 (94.0-98.6)
PPV	31.3 (17.3-48.4)	59.1 (38.5-77.5)	68.2 (47.4-84.5)
NPV	90.6 (86.2-93.9)	92.0 (88.0-94.9)	92.7 (88.9-93.9)
Accuracy	83.1 (78.2-87.3)	89.2 (85.0-92.5)	90.6 (86.6-93.7)

Abbreviations: PODEC= PreOperative Diagnostics in low-grade Endometrial Cancer, TVUS =transvaginal ultrasound, MRI= magnetic resonance imaging, MI= myometrial infiltration, CSI= cervical stroma invasion, PPV= positive predictive value, NPV= negative predictive value

When comparing TVUS and MRI with McNemar´s test for the assessment of MI the largest difference was found between MRI reader 1 and TVUS but there was also a difference between MRI reader 2 and TVUS. There was no statistically significant difference between the methods in the assessment of CSI. No significant difference was found between the two radiologists regarding assessment of deep MI or CSI.

Comments

In the NGEC revision of 2017, TVUS was recommended as an option for the preoperative assessment in low-grade endometrioid EC based on studies in which expert ultrasonographers showed reliable results in predicting deep MI[220,42]. TVUS is more readily available and less costly than MRI[220]. However, in the WSHCR there was a lack of gynecologists with specialized in ultrasound, why the PODEC study was initiated. The study is unique in the sense that it is the first study evaluating TVUS for the assessment of MI and CSI, performed by gynecologists with knowledge of TVUS, but not at expert level.

In the study, 32 gynecologists participated performing 1-46 examinations with TVUS each. The sensitivity varied between 27% and 100% for the five participating hospitals. This represented the clinical setting in which the study was performed and reflects a heterogenous group of TVUS operators of which some had more experience and skill than others. Interobserver analyses between the TVUS operators were not made. The overall performance of TVUS did not quite reach the results described in previous studies with expert ultrasonographers, were Alcazar *et al.*[38] showed a sensitivity 75% and specificity 86% in a pooled analysis of eight studies.

Some difficulties in the judgment of deep MI both with TVUS and MRI were anticipated in line with previous studies[221]. The cut-off of MI 50% is fairly straight forward to judge where the uterine wall is thick, but in the corners of the uterus at the tubal orifices this is more complex and challenging. Other difficulties in assessing the depth of invasion with both modalities can be related to other pathology of the uterus such as myomas and adenomyosis giving shadows on ultrasound and distorting the anatomy[221]. A very large uterus can be hard to examine with TVUS, because of a restricted depth of the examination field from the vaginal probe where MRI perform better. Another advantage of MRI in the preoperative assessment would be the possibility to cover the lymph nodes, whereas in TVUS a CT has to be added. On the other hand, TVUS is a dynamic examination where the movement between organs and structures can be utilized.

The assessment of CSI was poor with both TVUS and MRI, as compared to the pathology report. This may be attributable to the fact that in many cases the extension of tumor into cervical stroma is only a microscopic finding with no overt tumor to be seen. There was no statistically significant difference when comparing the methods.

Compared to MRI, TVUS found almost as many patients with deep MI, but overestimated MI more. This would result in more patients allocated to the high-risk group with an indication for lymph node assessment in the primary surgery. On the other hand, the risk of under-staging, that the patient needs to undergo a second surgery for re-staging with lymphadenectomy, is quite low. It can be argued that TVUS, performed by the gynecologist at the preoperative visit, is an acceptable first-line modality with MRI as second line in inconclusive or difficult cases.

5. Discussion

The outcomes generated in this thesis are discussed in comparison with related research in the Results and comments´ section. Below follow methodical considerations and a general discussion.

5.1 Methodological considerations

5.1.1 Cohort studies

Paper I-III were population-based register cohort studies and Paper IV was a prospective multicenter study comparing two methods. The cohort study as entity is seen as inferior to the gold standard, the randomized control study (RCT). Under many circumstances in cancer epidemiology, the RCT design is not applicable. The superiority of the RCT study is based on the blind randomization that removes bias. Although bias can be induced in RCTs through patient selection and thus reduce the representativeness and external validity of the studies. This may reduce the generalizability to the underlying population. Cohort studies can contribute to a broader knowledge of effects in real life but may be of different value depending on the design. In a retrospective single institution cohort, bias can be caused by a skewed selection of patients and additional bias can be induced by the outcome already known. In this context, the prospective population-based register can be judged reliable for studies, adding important information applicable to the underlying population to be assessed and treated.

With a robust and complete prospective registration concerning a complete population, the register reflects the real-life situation. It may be disputed whether to refer to a population-based register cohort study as prospective or retrospective. Some would say that it is a prospective study when data including outcomes are collected in a prospective manner. Although, according to definition when the research question is posed after the collection of data, the setting is historical or retrospective [222]. This is only wording that should not be given too much significance. Importantly, the continuous prospective data collection in the SQRGC is unbiased by the outcome and performed in a very complete manner.

Touching on ethics concerning storing patient data in registers: the mere existence of prospective registers must be motivated with a high rate of usage of the data for answering adequate research questions to improve patient care. Important findings can be made in large and complete databases such as the SQRGC. This is unique and incomparable to any other cohort trial setting. Additional value can be created by cross-linking registers for more information, made possible by personal identification numbers.

The sharp introduction of NGEC, on a specified date, mimics a randomization and is studied as before-after cohorts in Paper I-III. This is only possible when guidelines are strictly followed and adequately implemented in a country like Sweden, with a solid and equal health care system.

In Paper IV, a prospective multicenter method comparison study was conducted between TVUS and MRI for preoperative assessment of low-grade endometrial EC. In this study all subjects underwent both methods of assessment, that is they were their own controls.

5.1.2. Random error and study size

There is always uncertainty concerning the true measure of the effect of variables or interventions in a population. In all studies, there is the aim to achieve an as accurate as possible estimate to the true value. Efforts should be made to reduce both random and systematic errors.

Random error refers to the variability in the data by chance, or factors that cannot be explained. Statistics of variability tells us about the random error in the data. The confidence interval (CI) is a range of values around a point estimate and the narrower the more precise the estimate. The level of confidence is typically set to 95% indicating the true estimate to be within the interval 95% of the times the data collection and analysis were to be repeated. The larger the study, the more precise the estimate would be and thus the narrower CI. By increasing the study size, the estimate will become more precise.

The *p*-value is a statistic used in hypothesis testing commonly reported in studies. The level at which the null hypothesis can be rejected is indicated by the *p*-value. It is a measure of the strength of the statistical significance, meaning how true the findings are. As the *p*-value only tells us the magnitude of the statistical significance, we have also included the point estimated with CI for most

comparisons in the studies. This is considered to be clinically more relevant as it provides information the reader on the size and impact of the effect. For all studies the level of significance was set to 5%, which corresponds to a *p*-value of <0.05 for two-sided tests, in line with practice for most studies in the medical field.

If the results of a study lack statistical significance, there may still be an effect that was not found due to insufficient study size. A power calculation will estimate the size of the study needed to be able to show if a null hypothesis can be overthrown at the set significance level.

In Paper I, II & III, the size of the studies was dependent on the number of patients in the SQRGC for the years retrospectively studied. We believe there were enough patients for the analyses performed with the questions defined as there were equal or more patients than in similar register studies. For the prospective study PODEC, in Paper IV, the sample size estimation was mainly based on previous similar studies. Additionally, there was a power calculation performed based on a prevalence of 20% deep MI in low-grade endometrioid EC and with power set to 80%.

5.1.3 Systematic error

Systematic errors, or bias, can be introduced to the study in the selection of study participants (selection bias), measurement of study variables (information bias, misclassification and recall bias) and uncontrolled confounding factors. Increased cohort size cannot limit the effect of systematic errors and therefore these must be controlled in other ways[222].

For our studies in Paper I-III there was no selection of study participants as all patients with preoperatively early-stage EC in the WSHCR were included. Exclusions from the studies, for example for higher stages, were evenly distributed over the time periods. That is, the selection bias could be disregarded. In the PODEC study, Paper IV, exclusions made related to the possibility of undergoing MRI were assumed not to significantly affect the results of the study. The non-inclusions in the PODEC study were mainly due to pause of MRI examinations for vacations and we believe this did not interfere with the results either.

For the variables in Paper I-III, the prospective registration in SQRGC ensure no impact of the outcome on the variables registered. The bias of the researcher and research questions are minimized. There could have been some variations in the

registrations in SQRGC due to several different individuals taking part in the actual registration. Although, a quality control of the SQRGC has been undertaken and published with a high concordance[181]. Any variations in the registered variables were not related to each other or the outcome. This would be an example of non-differential misclassification which may dilute the effect measure but not skew it. Furthermore, when the medical records were reviewed in the course of the studies any obvious deviations were discovered and could be corrected for the analyses. Bias may also have been introduced in the medical records review, but was minimized by having a limited number of reviewers.

In Paper IV, there were many TVUS operators and a variation in the measurements and interpretation of findings was anticipated. We believe these variations were random and not repeatedly of the same character. The TVUS and MRI examinations were blinded to each other ensuring no bias between the TVUS operators and the two MRI readers.

Confounders, causing confusion of effects, are always present in studies. Some are obvious, but many are not known. In elucidating the confounders, the researcher needs to have an understanding of the causal effects, often deduced from previous studies and clinical knowledge. The prevention of confounding lies in the planning of a study where the firsthand recommended approaches are randomization, restriction or matching of subjects with similar values. We have not done any of this in our studies as the priority in these large register studies has been representativeness of the total population. The confounders occurring in this type of study have to be dealt with at the analysis stage. For example, stratification can be one way to go in making valid comparisons. Multivariable regression is another method to balance the confounders and this we have used in Papers I-III. In regression analyses the variables to include has to be chosen carefully not to overfit the models, but also to find the clinically relevant variables.

Missing data can be a major problem for the validity of analyses. Missing at random is less of a problem, only diluting the data, but missing not at random will incur a skewed result. Missing variables can be dealt with by analyzing the cause of missing data. In Paper I the missing data for peritoneal cytology and p53 was evenly distributed over the years, that is missing at random. For the variable flow cytometry however, the missing was for the year 2017, which was non-random missing. When finding this out we made a choice not to proceed with including

these data in the regression analysis for risk of recurrence. Overall, there was a low number of missing data for most variables.

5.1.4 Survival

Survival analyses were performed using the Kaplan-Meier method in which the proportion of survivors is calibrated at every death in the cohort[187].

Overall survival (OS), or observed survival, includes all patients in the cohort with the disease, in this case EC, and includes all deaths disregarding the cause of death. In an elderly population, such as the population of EC patients, there are many other causes of death in addition to death caused by EC why it can be argued that this measure is not the most adequate for estimating the cancer specific death rate. On the other hand, when making comparison of OS between large groups with the same age and traits that issue may be subordinate.

Net survival (NS) was calculated in Paper I with the Pohar Perme method in which death rates of the Swedish population were used for the estimation[188,189]. This is a relative survival (RS) measure, where other causes of death are taken into account and therefore can be considered a truer estimation of the survival related to the cancer diagnosis, in this respect EC. The RS measures are only possible in a setting where there is access to reliable comparable statistics on deaths as in Sweden through the national death register. Also, there can be issues in comparing relative survival data between countries when different types of estimations on deaths are used for the RS calculation. Thus, often the OS is used internationally in publications and presentations.

In Paper I, the choice was to display both OS and NS, but in Paper II only OS were included in the publication although we had analyzed NS as well. In an elderly cohort, such as women with EC, there is the non-negligible competing event of death from other causes than EC and preferably this will be taken into account when estimating survival. Especially when the disease itself has a relatively low mortality, such as in endometrioid EC, the effect of death of other causes will affect the OS to a relatively large proportion. This is why the NS may be the most appropriate measure for survival. Nonetheless, this measure needs age-standardized cause of death data, and this is not available everywhere. For international comparisons OS is more often used and for diseases such as more aggressive cancer types the effect of competing death of other causes interfere less.

The follow-up period for recurrence and survival in Paper I, II and III was truncated at five years. This is the period commonly used in the context of cancer. Although some recurrences do occur after the five-year period, the majority occur within the first three years[144].

5.1.5 Diagnostic accuracy

The accuracy of a method is the proportion of correctly classified cases. For a perfect method this would be 100%, which is never the case in clinical methods, but the aim is to reach as high as possible. Sensitivity defines the proportion of true positives and the complementary measure specificity defines the true negative. In the PODEC study in Paper IV, a high sensitivity was judged most important, not to miss any cases with deep MI. Although the specificity had to be reasonable, since an overestimation of the MI led to an unnecessary surgery with lymphadenectomy.

5.2 General discussion

For the cancer patient in general, the overall goal is cure. Besides surviving cancer, quality of life is of utmost importance. In EC there are many long-term survivors, and adverse effects of treatment should be minimized. Importantly, we should not inflict harm by treatments with limited effect, this goes back to the non-maleficence of the Hippocratic oath. Major steps in EC treatment have been taken in the last years. There is a rapid evolvement of new findings in prognostic and treatment-predictive factors leading towards individually tailored treatment in EC with an anticipated gain for the patient with an improved quality of life.

Large population-based studies are important to follow-up on changes and interventions in treatment guidelines. Sweden offers an ideal setting for this type of research due to comprehensive registers based on unique personal identification numbers. Furthermore, due to the public health system there is equal access to advanced medical care regardless of financial status. There is also a great adherence to guidelines in treatment of cancer, which is proven beneficial for the outcome [223]. These factors contribute to an ideal study base when studying effects of treatment and changes in care.

The shift in treatment guidelines, with the implementation of the Swedish NGEC in the WSHCR, resulted in improved survival of non-endometrioid EC and maintained survival in endometrioid EC when PPLND was introduced for staging

in the high-risk group and de-escalation of adjuvant radiotherapy. Although the lymphadenectomy surgery implied a higher surgical complication rate and incurred a risk of lymphedema this was beneficial for the patients in terms of prognosis but also importantly, spared the side-effects of radiation.

Adjuvant therapy in stage I EC is under debate. For many years adjuvant therapy with radiation has been administered based on risk factors of the tumor. However, studies have failed to prove survival benefits. On the contrary, the not primarily radiated patients have an advantage in the recurrent situation. In our study, the postoperative radiation was reserved for stage III after the NGEC implementation with favorable outcome. Interestingly, a Danish study showed similar results in a large register-based follow-up on the decision in 2005 not to give adjuvant radiotherapy to adequately staged high risk stage I. They found no increase in locoregional recurrences nor impaired survival in comparison to a historic cohort[224].

In our studies, the total EC cohort from the years 2010-2017 was divided into endometrioid and non-endometrioid EC cohorts for the analyses for Papers I and II. The rationale for this grouping was the rather different tumor characteristics of the two types. All EC are often clumped together in studies, and it is challenging to sort out how risk factors are related to the different types. In some studies, there are only low risk, that is the low-grade endometrioid, and in other studies there is a mix of high-grade endometrioid EC and non-endometrioid denoted high-risk. Our belief is that high-grade endometrioid do not quite behave as non-endometrioid EC and as mentioned we have allocated them to the endometrioid cohort. Further advances in molecular findings will guide us on how to handle and interpret the different types of EC in the future. Anyhow, there is clearly a difference in behavior between the endometrioid and non-endometrioid EC concerning recurrence patterns as well as recurrence rates and survival as shown in Papers I-II.

Considering recurrence to be a result of occult residual disease after primary treatment, it is logical to think that for the more aggressive types of tumors the recurrence presents as an overt tumor faster than in the more indolent types. The endometrioid had somewhat longer time to recurrence than the non-endometroid in our studies in Paper I-II. However, we found in the vaginal recurrences, a manifestation more prone to be of the low-grade tumor, the time to recurrence to be the shortest. This is hard to explain, but to speculate: there may have been undetected vaginal implantation at diagnosis to some extent? Or can it be a result of

contamination of tumor cells to the vagina at surgery? This question may be further explored in the future.

Lymphadenectomy was associated with improved DFS in the multivariable analysis of the non-endometrioid EC cohort presented in Paper II. The confounding effects of age, stage and adjuvant treatment were considered in the analysis why we believe there is a true effect shown. This re-opens the question as to whether there can be a therapeutic effect of removing occult disease in the lymph nodes. Whether this is the matter or not has to be evaluated in further large studies.

Lymphadenectomy was found to be an independent risk factor for complications in our study of Paper III, but not for recurrences in Paper I. Since the consequences of lymphadenectomy besides surgical complications also incur a risk of lymphedema the evolvement towards an adequate staging with the sentinel lymph node procedure is advantageous. As previously mentioned, the sentinel lymph node concept is proven as least as good or better than lymphadenectomy for the surgical staging in EC[65,50]. Although, this raises the question of whether to proceed with paraaortic lymphadenectomy in the case of positive pelvic sentinel nodes as the risk can be as high as 50% for also having positive paraaortic nodes[50]. The paraaortic lymph node status may guide the planning of adjuvant radiation. The alternative to restaging surgery with paraaortic lymphadenectomy would be radiology with CT, MRI although the performance is poor in detecting non-enlarged positive lymph nodes. Proposals have been made to use PET-CT, although the method has not more than 70% sensitivity[45,47]. An argument for restaging surgery with paraaortic node removal, would be a possible positive effect of removing occult tumor.

Recurrence rates and patterns should be further investigated in the era of the sentinel node concept. A reduced rate of recurrences in pelvic nodes may be anticipated as the sentinel node concept implies a precise removal of the most exposed nodes that may previously have been left behind.

Importantly, there are no findings in our studies in Paper I, II and III overthrowing the recommendation of MIS as the preferred method for primary surgery to all uterine confined EC. Rather the risk of surgical complications was reduced with MIS compared to open surgery (Paper III). Moreover, in Paper I the surgical technique was not found to be a risk factor for recurrence.

Complications to surgery should be avoided to the greatest extent possible. The

cancer diagnosis implies a strong indication for surgery, even when the patient has an elevated risk for complications, in contrast to surgery on benign indication. In the EC population of patients, the high BMI requires special consideration as this is frequent among the group. In Paper III, we showed that obesity was associated with a higher risk of surgical complications. In addition, many patients were elderly and had intercurrent diseases, but we were somewhat surprised that the Charlson's scores were not on average higher. Interestingly, the risk of surgical complications did not seem to be affected by the patients age or comorbidities, in our study. This finding was maybe biased by the selection of patients for the advanced surgery, where the oldest and most frail patients were not considered for PPLND or even lymphadenectomy at all. Another question would be if we had a large enough cohort to show an effect of a higher Charlons score as there were few individuals with high scores and an overall low rate of complications. Nevertheless, the development of MIS to robotic surgery has been beneficial for obese and frail patients and nowadays almost all patients can be offered surgery, the recommended primary treatment in EC.

Preoperative evaluation of low-grade endometrial EC for the allocation into risk groups for surgery is needed in a setting where the high-risk group is referred to a tertiary center for surgery with lymph node assessment. One can argue that the introduction of the sentinel node concept for all EC would diminish the need for preoperative assessment. Although, that approach incurs a centralization of all EC surgery to tertiary centers, where the sentinel node procedure is performed, and that may not be feasible. In Paper IV, we suggest that TVUS has an accuracy acceptable as the first line modality for the preoperative decision making in low-grade endometrioid EC, regarding deep MI or not. This method is at easy access and low extra cost when performed by the gynecologist at the preoperative visit. If there are difficulties in the judgement, we recommend a referral for MRI according to a defined protocol and with the possibility of expert review at a tertiary center and discussion at MDT.

6. Conclusions

The conclusions of this thesis investigating recurrence, survival, surgical complications and preoperative diagnostics in EC in a complete population-based cohort were:

- The recurrence rate was low in endometrioid (8%) and high in non-endometrioid EC (29%) (Papers I and II).
- In endometrioid EC isolated vaginal recurrences comprised just above a quarter of the recurrences and a third of the recurrences were distant (Paper I).
- In non-endometrioid EC localized recurrences were infrequent and more than half of the recurrences were abdominal including carcinomatosis (Paper II).
- Age, stage and received primary treatment were found to be independent risk factors for recurrence in endometrioid EC (Paper I).
- Survival was superior in endometrioid EC compared to non-endometrioid EC (Paper I and II).
- The survival was excellent when no recurrence occurred in both endometrioid and non-endometrioid EC (Papers I and II).
- The survival was negatively affected by recurrence (Papers I and II).
- Survival for isolated vaginal recurrence was superior to all other recurrences (Paper I).
- There was a significant improvement in survival for non-endometrioid EC after the implementation of NGEC introducing PPLND in the high-risk group and de-escalation of adjuvant radiotherapy (Paper II).
- Lymphadenectomy, patient age and tumor stage were found to be significant independent factors for DFS in non-endometrioid EC (Paper II).
- Surgical complications of higher grade are rare in EC surgery (Paper III).
- Lymphadenectomy and obesity increased the risk and MIS reduced the risk of surgical complications in EC surgery (Paper III).
- Assessment of deep MI with TVUS performed by the gynecologists involved in EC treatment has an acceptable accuracy and may be sufficient as a first-line modality in the re-operative staging of low-grade EC (Paper IV).

7. Future perspectives

In the coming decade it will be of utmost importance to continue the research on EC prognostic risk factors in an attempt to establish optimal strategies for treatments. It may be proposed to form more precise algorithms for predicting recurrence in EC and thereby forming personalized treatment protocols. A hot topic is the molecular tumor biomarkers, as prognostic factors and treatment predictive factors.

The intention in our research group is to further investigate recurrence and survival in the context of the proposed tumor biomarkers. We have, with the database based on SQRGC for the studies in Papers I and II, a unique opportunity to use this data with the addition of a new review of the histopathology including LVSI, extended immunohistochemistry and new molecular analyses.

Also, the time to recurrence and recurrence localization in relation to tumor biomarkers are of special interest. There are for example indications of a shorter time to recurrence and more locoregional and isolated vaginal recurrences in MMRd [225]. In a study from Backes *et al,* the group of high intermediate risk patients with deficient MMR were found to be associated with increased rates of recurrence compared with those with intact MMR[226]. This may entail new alternatives for adjuvant treatments including immunotherapy and more studies are to be expected.

Further investigation on the recently introduced sentinel lymph node concept, replacing PPLND, is warranted. It is important to make use of complete population-based registers with adequate and valid data on follow-up and oncological outcome. A continuous evolvement of the variables in the SQRGC to adapt to new methods is necessary to facilitate evaluations. In a couple of years, we believe we will have enough follow-up time to evaluate if the improvement in survival in the non-endometrioid cohort found in Paper II, still stands when PPLND is replaced by the sentinel node procedure. Furthermore, it will be interesting to study the recurrence localization following sentinel node procedures. Interestingly, How *et al.* showed a reduced rate of pelvic side-wall recurrences when the sentinel nodes were taken, and this is highly intriguing[227]. The rate of paraaortic lymph node recurrences may also be investigated in patients with positive sentinel

lymph nodes in the pelvis. According to Aloisi *et al.* paraaortic lymph node recurrences are rare in patients primarily in FIGO stage IIIC1 based on only pelvic lymphadenectomy, where no paraaortic lymphadenectomy was done [64].

Regarding lymph node assessment, there may be new radiological methods to be introduced in the preoperative setting, rendering lymph node dissection or sentinel lymph node unnecessary[228,229]. We are currently investigating the use of superparamagnetic iron oxide (SPIO) MRI for pre-operative staging assessment in EC. The aim is to investigate if SPIO MRI can localize the sentinel node as correlated to ICG in robotic surgery and to evaluate if metastatic lymph nodes can be predicted. Results of this feasibility study are expected in the coming year.

Surgical complications may be easier to study in the future as there is now a national registration of surgical complications in the SQRGC. It is anticipated, that the surgical complication rate in EC decreases as the sentinel lymph node procedure has replaced lymphadenectomy and the rate of MIS by robotic surgery is expanded.

Quality of life-studies are needed continuously in EC to evaluate the changes in diagnostics and treatment. Importantly, there is a need to involve the patient experiences to assure a development of treatment guidelines in the right direction.

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(Photo: L Wiman)

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References

1. Nationellt vårdprogram endometricancer. Sweden: RCC; 2011.
2. Årsrapport Svenska Kvalitetsregistret för Gynekologisk Cancer (SQRGC) 2022.
3. WHO/IARC. Corpus uteri, Globocan 2020; https://gco.iarc.fr/today/data/factsheets/cancers/24-Corpus-uteri-fact-sheet.pdf.
4. Lortet-Tieulent J, Ferlay J, Bray F, Jemal A. International Patterns and Trends in Endometrial Cancer Incidence, 1978-2013. J Natl Cancer Inst. Vol 110. 2017/10/19 ed2018.
5. Sheikh MA, Althouse AD, Freese KE, et al. USA Endometrial Cancer Projections to 2030: should we be concerned? Future Oncology. 2014;10(16):2561-2568.
6. WHO/IARC. Corpus uteri, Nordcan; https://gco.iarc.fr/media/nordcan/factsheets/92/en/countries/0/corpus_uteri-200-nordcan_countries-0.pdf
7. Pennant ME, Mehta R, Moody P, et al. Premenopausal abnormal uterine bleeding and risk of endometrial cancer. BJOG. 2017;124(3):404-411.
8. Nationellt vårdprogram livmoderkroppscancer. Sweden: RCC; 2021.
9. Bokhman JV. Two pathogenetic types of endometrial carcinoma. Gynecologic oncology. 1983;15(1):10-17.
10. Kurman RJ, Visvanathan K, Shih Ie M. Bokhman's dualistic model of endometrial carcinoma. Revisited. Gynecologic oncology. 2013;129(2):271-272.
11. Renehan AG, Roberts DL, Dive C. Obesity and cancer: pathophysiological and biological mechanisms. Arch Physiol Biochem. 2008;114(1):71-83.
12. Purdie DM, Green AC. Epidemiology of endometrial cancer. Best Pract Res Clin Obstet Gynaecol. 2001;15(3):341-354.
13. Karlsson B GS, Wikland M. Transvaginal ulttrasonography of the endometrium in women with postmenopausal bleeding - a nordic multicenter study. Am J Gynecol Obstet. 1995;172(5):1488-1494.
14. Dijkhuizen FP, Mol BW, Brolmann HA, Heintz AP. The accuracy of endometrial sampling in the diagnosis of patients with endometrial carcinoma and hyperplasia: a meta-analysis. Cancer. 2000;89(8):1765-1772.
15. Alfhaily F, Ewies AA. The first-line investigation of postmenopausal bleeding: transvaginal ultrasound scanning and endometrial biopsy may be enough. Int J Gynecol Cancer. 2009;19(5):892-895.
16. Youssif SN, McMillan DL. Outpatient endometrial biopsy: the pipelle. Br J Hosp Med. 1995;54(5):198-201.
17. Lacey JV, Jr., Chia VM. Endometrial hyperplasia and the risk of progression to carcinoma. Maturitas. 2009;63(1):39-44.
18. Kurman RJ, Kaminski PF, Norris HJ. The behavior of endometrial hyperplasia. A long-term study of "untreated" hyperplasia in 170 patients. Cancer. 1985;56(2):403-412.
19. Nationellt vårdprogram endometriecancer. Sweden: RCC; 2017.
20. Concin N, Matias-Guiu X, Vergote I, et al. ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma. Int J Gynecol Cancer. 2021;31(1):12-39.
21. Creutzberg CL, van Putten WL, Warlam-Rodenhuis CC, et al. Outcome of high-risk stage IC, grade 3, compared with stage I endometrial carcinoma patients: the Postoperative Radiation Therapy in Endometrial Carcinoma Trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2004;22(7):1234-1241.
22. Keys HM, Roberts JA, Brunetto VL, et al. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study. Gynecologic oncology. 2004;92(3):744-751.
23. Mariani A, Dowdy SC, Cliby WA, et al. Prospective assessment of lymphatic dissemination in endometrial cancer: a paradigm shift in surgical staging. Gynecologic oncology. 2008;109(1):11-18.

24. Frumovitz M, Singh DK, Meyer L, et al. Predictors of final histology in patients with endometrial cancer. Gynecologic oncology. 2004;95(3):463-468.

25. Leitao MM, Jr., Kehoe S, Barakat RR, et al. Accuracy of preoperative endometrial sampling diagnosis of FIGO grade 1 endometrial adenocarcinoma. Gynecologic oncology. 2008;111(2):244-248.

26. Gayar OH, Patel S, Schultz D, Mahan M, Rasool N, Elshaikh MA. The impact of tumor grade on survival end points and patterns of recurrence of 949 patients with early-stage endometrioid carcinoma: a single institution study. Int J Gynecol Cancer. 2014;24(1):97-101.

27. Announcements. International Federation of Gynecology and Obstetrics (FIGO) stages—1988 revision. Gynecologic oncology. 1989;35:125-127.

28. Barlin JN, Soslow RA, Lutz M, et al. Redefining stage I endometrial cancer: incorporating histology, a binary grading system, myometrial invasion, and lymph node assessment. Int J Gynecol Cancer. 2013;23(9):1620-1628.

29. WHO Classifications of Tumours Editorial Board, Female genital tumours. 5 ed. Lyon: IARC 2020. Blue book; No. 4.

30. Brinton LA, Felix AS, McMeekin DS, et al. Etiologic heterogeneity in endometrial cancer: evidence from a Gynecologic Oncology Group trial. Gynecologic oncology. 2013;129(2):277-284.

31. Morice P, Leary A, Creutzberg C, Abu-Rustum N, Darai E. Endometrial cancer. Lancet. 2016;387(10023):1094-1108.

32. Creasman WT, Morrow CP, Bundy BN, Homesley HD, Graham JE, Heller PB. Surgical pathologic spread patterns of endometrial cancer: A gynecologic oncology group study. Cancer. 1987;60(8 S):2035-2041.

33. Morrow CP, Bundy BN, Kurman RJ, et al. Relationship between Surgical-Pathological Risk Factors and Outcome in Clinical Stage I and II Carcinoma of the Endometrium: A Gynecologic Oncology Group Study. Gynecologic oncology. 1991;40:55-65.

34. Pecorelli S. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics. 2009;105(2):103-104.

35. Regionala vårdprogram, Gynekologiska tumörsjukdomar, Corpuscancer. Onkologiskt centrum 2005.

36. Mariani A, Dowdy SC, Cliby WA, et al. Prospective assessment of lymphatic dissemination in endometrial cancer: A paradigm shift in surgical staging. Gynecologic oncology. 2008;109(1):11-18.

37. Savelli L, Ceccarini M, Ludovisi M, et al. Preoperative local staging of endometrial cancer: transvaginal sonography vs. magnetic resonance imaging. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2008;31(5):560-566.

38. Alcazar JL, Gaston B, Navarro B, Salas R, Aranda J, Guerriero S. Transvaginal ultrasound versus magnetic resonance imaging for preoperative assessment of myometrial infiltration in patients with endometrial cancer: a systematic review and meta-analysis. Journal of gynecologic oncology. 2017;28(6):e86.

39. Fanning J, Alvarez PM, Tsukada Y, Piver MS. Prognostic significance of the extent of cervical involvement by endometrial cancer. Gynecologic oncology. 1991;40(1):46-47.

40. Elshaikh MA, Al-Wahab Z, Mahdi H, et al. Recurrence patterns and survival endpoints in women with stage II uterine endometrioid carcinoma: a multi-institution study. Gynecologic oncology. 2015;136(2):235-239.

41. Brown AK, Madom L, Moore R, Granai CO, DiSilvestro P. The prognostic significance of lower uterine segment involvement in surgically staged endometrial cancer patients with negative nodes. Gynecologic oncology. 2007;105(1):55-58.

42. Epstein E, Blomqvist L. Imaging in endometrial cancer. Best Pract Res Clin Obstet Gynaecol. 2014;28(5):721-739.

43. Nasioudis D, Sakamuri S, Ko EM, et al. Radical hysterectomy is not associated with a survival benefit for patients with stage II endometrial carcinoma. Gynecologic oncology. 2020;157(2):335-339.

44. Phelippeau J, Koskas M. Impact of Radical Hysterectomy on Survival in Patients with Stage 2 Type1 Endometrial Carcinoma: A Matched Cohort Study. Ann Surg Oncol. 2016;23(13):4361-4367.

45. Kim HJ, Cho A, Yun M, Kim YT, Kang WJ. Comparison of FDG PET/CT and MRI in lymph node staging of endometrial cancer. Ann Nucl Med. 2016;30(2):104-113.
46. Fasmer KE, Gulati A, Dybvik JA, et al. Preoperative pelvic MRI and 2-[(18)F]FDG PET/CT for lymph node staging and prognostication in endometrial cancer-time to revisit current imaging guidelines? Eur Radiol. 2023;33(1):221-232.
47. Fasmer KE, Gulati A, Dybvik JA, et al. Preoperative 18F-FDG PET/CT tumor markers outperform MRI-based markers for the prediction of lymph node metastases in primary endometrial cancer. Eur Radiol. 2020;30(5):2443-2453.
48. Mariani A, Keeney GL, Aletti G, Webb MJ, Haddock MG, Podratz KC. Endometrial carcinoma: paraaortic dissemination. Gynecologic oncology. 2004;92(3):833-838.
49. AlHilli MM, Mariani A. The role of para-aortic lymphadenectomy in endometrial cancer. Int J Clin Oncol. 2013;18(2):193-199.
50. Persson J, Salehi S, Bollino M, Lonnerfors C, Falconer H, Geppert B. Pelvic Sentinel lymph node detection in High-Risk Endometrial Cancer (SHREC-trial)-the final step towards a paradigm shift in surgical staging. Eur J Cancer. 2019;116:77-85.
51. Salehi S, Åvall-Lundqvist E, Legerstam B, Carlson JW, Falconer H. Robot-assisted laparoscopy versus laparotomy for infrarenal paraaortic lymphadenectomy in women with high-risk endometrial cancer: A randomised controlled trial. European Journal of Cancer. 2017;79:81-89.
52. Wedin M, Stalberg K, Marcickiewicz J, et al. Incidence of lymphedema in the lower limbs and lymphocyst formation within one year of surgery for endometrial cancer: A prospective longitudinal multicenter study. Gynecologic oncology. 2020;159(1):201-208.
53. Wedin M, Stalberg K, Marcickiewicz J, et al. Risk factors for lymphedema and method of assessment in endometrial cancer: a prospective longitudinal multicenter study. Int J Gynecol Cancer. 2021.
54. Wedin M, Stalberg K, Marcickiewicz J, et al. Impact of lymphadenectomy and lymphoedema on health-related quality of life 1 year after surgery for endometrial cancer. A prospective longitudinal multicentre study. BJOG. 2021.
55. Volpi L, Sozzi G, Capozzi VA, et al. Long term complications following pelvic and para-aortic lymphadenectomy for endometrial cancer, incidence and potential risk factors: a single institution experience. Int J Gynecol Cancer. 2019;29(2):312-319.
56. Colombo N, Creutzberg C, Amant F, et al. ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer: diagnosis, treatment and follow-up. Ann Oncol. 2016;27(1):16-41.
57. Cragun JM, Havrilesky LJ, Calingaert B, et al. Retrospective analysis of selective lymphadenectomy in apparent early-stage endometrial cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2005;23(16):3668-3675.
58. Chan JK, Cheung MK, Huh WK, et al. Therapeutic role of lymph node resection in endometrioid corpus cancer: a study of 12,333 patients. Cancer. 2006;107(8):1823-1830.
59. Todo Y, Kato H, Kaneuchi M, Watari H, Takeda M, Sakuragi N. Survival effect of para-aortic lymphadenectomy in endometrial cancer (SEPAL study): a retrospective cohort analysis. Lancet. 2010;375(9721):1165-1172.
60. Eggemann H, Ignatov T, Kaiser K, Burger E, Costa SD, Ignatov A. Survival advantage of lymphadenectomy in endometrial cancer. Journal of cancer research and clinical oncology. 2016;142(5):1051-1060.
61. Kitchener H, Swart AM, Qian Q, Amos C, Parmar MK, group As. Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study. Lancet. 2009;373(9658):125-136.
62. Panici PB, Basile S, Maneschi F, et al. Systematic pelvic lymphadenectomy vs no lymphadenectomy in early-stage endometrial carcinoma: Randomized clinical trial. Journal of the National Cancer Institute. 2008;100(23):1707-1716.
63. Frost JA, Webster KE, Bryant A, Morrison J. Lymphadenectomy for the management of endometrial cancer. The Cochrane database of systematic reviews. 2017;10:Cd007585.
64. Aloisi A, Casanova JM, Tseng JH, et al. Patterns of FIRST recurrence of stage IIIC1 endometrial cancer with no PARAAORTIC nodal assessment. Gynecologic oncology. 2018;151(3):395-400.
65. Zahl Eriksson AG, Ducie J, Ali N, et al. Comparison of a sentinel lymph node and a selective lymphadenectomy algorithm in patients with endometrioid endometrial carcinoma and limited myometrial invasion. Gynecologic oncology. 2016;140(3):394-399.

66. Grassi T, Mariani A, Cibula D, et al. A prospective multicenter international single-arm observational study on the oncological safety of the sentinel lymph node algorithm in stage I intermediate-risk endometrial cancer (SELECT, SEntinel Lymph node Endometrial Cancer Trial). Int J Gynecol Cancer. 2020;30(10):1627-1632.

67. Holloway RW, Abu-Rustum NR, Backes FJ, et al. Sentinel lymph node mapping and staging in endometrial cancer: A Society of Gynecologic Oncology literature review with consensus recommendations. Gynecologic oncology. 2017;146(2):405-415.

68. Darai E, Dubernard G, Bats AS, et al. Sentinel node biopsy for the management of early stage endometrial cancer: long-term results of the SENTI-ENDO study. Gynecologic oncology. 2015;136(1):54-59.

69. Ducie JA, Eriksson AGZ, Ali N, et al. Comparison of a sentinel lymph node mapping algorithm and comprehensive lymphadenectomy in the detection of stage IIIC endometrial carcinoma at higher risk for nodal disease. Gynecologic oncology. 2017;147(3):541-548.

70. Rossi EC, Kowalski LD, Scalici J, et al. A comparison of sentinel lymph node biopsy to lymphadenectomy for endometrial cancer staging (FIRES trial): a multicentre, prospective, cohort study. Lancet Oncol. 2017;18(3):384-392.

71. Ballester M, Dubernard G, Lécuru F, et al. Detection rate and diagnostic accuracy of sentinel-node biopsy in early stage endometrial cancer: A prospective multicentre study (SENTI-ENDO). The Lancet Oncology. 2011;12(5):469-476.

72. Schlappe BA, Weaver AL, McGree ME, et al. Multicenter study comparing oncologic outcomes after lymph node assessment via a sentinel lymph node algorithm versus comprehensive pelvic and paraaortic lymphadenectomy in patients with serous and clear cell endometrial carcinoma. Gynecologic oncology. 2020;156(1):62-69.

73. Basaran D, Bruce S, Aviki EM, et al. Sentinel lymph node mapping alone compared to more extensive lymphadenectomy in patients with uterine serous carcinoma. Gynecologic oncology. 2020;156(1):70-76.

74. Rossi EC, Jackson A, Ivanova A, Boggess JF. Detection of sentinel nodes for endometrial cancer with robotic assisted fluorescence imaging: cervical versus hysteroscopic injection. Int J Gynecol Cancer. 2013;23(9):1704-1711.

75. Geppert B, Lonnerfors C, Bollino M, Arechvo A, Persson J. A study on uterine lymphatic anatomy for standardization of pelvic sentinel lymph node detection in endometrial cancer. Gynecologic oncology. 2017;145(2):256-261.

76. Luhrs O, Bollino M, Ekdahl L, Lonnerfors C, Geppert B, Persson J. Similar distribution of pelvic sentinel lymph nodes and nodal metastases in cervical and endometrial cancer. A prospective study based on lymphatic anatomy. Gynecologic oncology. 2022;165(3):466-471.

77. Backes FJ, Cohen D, Salani R, et al. Prospective clinical trial of robotic sentinel lymph node assessment with isosulfane blue (ISB) and indocyanine green (ICG) in endometrial cancer and the impact of ultrastaging (NCT01818739). Gynecologic oncology. 2019;153(3):496-499.

78. Frumovitz M, Plante M, Lee PS, et al. Near-infrared fluorescence for detection of sentinel lymph nodes in women with cervical and uterine cancers (FILM): a randomised, phase 3, multicentre, non-inferiority trial. Lancet Oncol. 2018;19(10):1394-1403.

79. Burg LC, Hengeveld EM, In 't Hout J, Bulten J, Bult P, Zusterzeel PLM. Ultrastaging methods of sentinel lymph nodes in endometrial cancer - a systematic review. Int J Gynecol Cancer. 2021;31(5):744-753.

80. Kim CH, Soslow RA, Park KJ, et al. Pathologic ultrastaging improves micrometastasis detection in sentinel lymph nodes during endometrial cancer staging. Int J Gynecol Cancer. 2013;23(5):964-970.

81. Barlin JN, Khoury-Collado F, Kim CH, et al. The importance of applying a sentinel lymph node mapping algorithm in endometrial cancer staging: beyond removal of blue nodes. Gynecologic oncology. 2012;125(3):531-535.

82. Bollino M, Geppert B, Lonnerfors C, Falconer H, Salehi S, Persson J. Pelvic sentinel lymph node biopsy in endometrial cancer-a simplified algorithm based on histology and lymphatic anatomy. Int J Gynecol Cancer. 2020;30(3):339-345.

83. Backes FJ, Felix AS, Plante M, et al. Sentinel lymph node (SLN) isolated tumor cells (ITCs) in otherwise stage I/II endometrioid endometrial cancer: To treat or not to treat? Gynecologic oncology. 2021;161(2):347-352.

84. Han KH, Park NH, Kim HS, Chung HH, Kim JW, Song YS. Peritoneal cytology: a risk factor of recurrence for non-endometrioid endometrial cancer. Gynecologic oncology. 2014;134(2):293-296.
85. Ørtoft G, Lausten-Thomsen L, Høgdall C, Hansen ES, Dueholm M. Lymph-vascular space invasion (LVSI) as a strong and independent predictor for non-locoregional recurrences in endometrial cancer: a Danish Gynecological Cancer Group Study. Journal of gynecologic oncology. 2019;30(5):e84.
86. Weinberg LE, Kunos CA, Zanotti KM. Lymphovascular space invasion (LVSI) is an isolated poor prognostic factor for recurrence and survival among women with intermediate- to high-risk early-stage endometrioid endometrial cancer. Int J Gynecol Cancer. 2013;23(8):1438-1445.
87. dos Reis R, Burzawa JK, Tsunoda AT, et al. Lymphovascular Space Invasion Portends Poor Prognosis in Low-Risk Endometrial Cancer. Int J Gynecol Cancer. 2015;25(7):1292-1299.
88. Stalberg K, Bjurberg M, Borgfeldt C, et al. Lymphovascular space invasion as a predictive factor for lymph node metastases and survival in endometrioid endometrial cancer - a Swedish Gynecologic Cancer Group (SweGCG) study. Acta Oncol. 2019;58(11):1628-1633.
89. Bosse T, Peters EE, Creutzberg CL, et al. Substantial lymph-vascular space invasion (LVSI) is a significant risk factor for recurrence in endometrial cancer--A pooled analysis of PORTEC 1 and 2 trials. Eur J Cancer. 2015;51(13):1742-1750.
90. Veade AE, Foote J, Ehrisman J, et al. Associations between lymphovascular space invasion, nodal recurrence, and survival in patients with surgical stage I endometrioid endometrial adenocarcinoma. World J Surg Oncol. 2019;17(1):80.
91. Ureyen I, Karalok A, Turkmen O, et al. Factors predicting recurrence in patients with stage IA endometrioid endometrial cancer: what is the importance of LVSI? Arch Gynecol Obstet. 2020;301(3):737-744.
92. Tortorella L, Restaino S, Zannoni GF, et al. Substantial lymph-vascular space invasion (LVSI) as predictor of distant relapse and poor prognosis in low-risk early-stage endometrial cancer. Journal of gynecologic oncology. 2021;32(2):e11.
93. Abu-Rustum NR, Zhou Q, Gomez JD, et al. A nomogram for predicting overall survival of women with endometrial cancer following primary therapy: toward improving individualized cancer care. Gynecologic oncology. 2010;116(3):399-403.
94. Ytre-Hauge S, Husby JA, Magnussen IJ, et al. Preoperative tumor size at MRI predicts deep myometrial invasion, lymph node metastases, and patient outcome in endometrial carcinomas. Int J Gynecol Cancer. 2015;25(3):459-466.
95. Mariani A, Webb MJ, Keeney GL, Haddock MG, Calori G, Podratz KC. Low-risk corpus cancer: Is lymphadenectomy or radiotherapy necessary? American Journal of Obstetrics and Gynecology. 2000;182(6):1506-1519.
96. Nwachukwu C, Baskovic M, Von Eyben R, et al. Recurrence risk factors in stage IA grade 1 endometrial cancer. Journal of gynecologic oncology. 2021;32(2):e22.
97. Canlorbe G, Bendifallah S, Laas E, et al. Tumor Size, an Additional Prognostic Factor to Include in Low-Risk Endometrial Cancer: Results of a French Multicenter Study. Ann Surg Oncol. 2016;23(1):171-177.
98. Trovik J, Wik E, Werner HM, et al. Hormone receptor loss in endometrial carcinoma curettage predicts lymph node metastasis and poor outcome in prospective multicentre trial. Eur J Cancer. 2013;49(16):3431-3441.
99. Vrede SW, van Weelden WJ, Visser NCM, et al. Immunohistochemical biomarkers are prognostic relevant in addition to the ESMO-ESGO-ESTRO risk classification in endometrial cancer. Gynecologic oncology. 2021;161(3):787-794.
100. Post CCB, Stelloo E, Smit V, et al. Prevalence and Prognosis of Lynch Syndrome and Sporadic Mismatch Repair Deficiency in Endometrial Cancer. J Natl Cancer Inst. 2021;113(9):1212-1220.
101. O'Malley DM, Bariani GM, Cassier PA, et al. Pembrolizumab in Patients With Microsatellite Instability-High Advanced Endometrial Cancer: Results From the KEYNOTE-158 Study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2022;40(7):752-761.
102. Njolstad TS, Trovik J, Hveem TS, et al. DNA ploidy in curettage specimens identifies high-risk patients and lymph node metastasis in endometrial cancer. Br J Cancer. 2015;112(10):1656-1664.

103. Sorbe B. Prognostic importance of DNA ploidy in non-endometrioid, high-risk endometrial carcinomas. Oncology Letters. 2016;11(3):2283-2289.

104. Stalberg K, Kjolhede P, Bjurberg M, Borgfeldt C, Dahm-Kahler P, Falconer H, et al. Risk factors for lymph. node metastases in women with endometrial cancer:; A population based nation wide register study - on behalf of the Swedish Gynecological Canser Group. Int. J. Cancer 2017;140(12):2693-2700.

105. The Cancer Genome Atlas Research Network, Kandoth C, Schultz N, et al. Integrated genomic characterization of endometrial carcinoma. Nature. 2013;497(7447):67-73.

106. Stelloo E, Nout RA, Osse EM, et al. Improved Risk Assessment by Integrating Molecular and Clinicopathological Factors in Early-stage Endometrial Cancer-Combined Analysis of the PORTEC Cohorts. Clin Cancer Res. 2016;22(16):4215-4224.

107. Talhouk A, McConechy MK, Leung S, et al. Confirmation of ProMisE: A simple, genomics-based clinical classifier for endometrial cancer. Cancer. 2017;123(5):802-813.

108. Bosse T, Nout RA, McAlpine JN, et al. Molecular Classification of Grade 3 Endometrioid Endometrial Cancers Identifies Distinct Prognostic Subgroups. Am J Surg Pathol. 2018;42(5):561-568.

109. Vermij L, Smit V, Nout R, Bosse T. Incorporation of molecular characteristics into endometrial cancer management. Histopathology. 2020;76(1):52-63.

110. Leon-Castillo A, de Boer SM, Powell ME, et al. Molecular Classification of the PORTEC-3 Trial for High-Risk Endometrial Cancer: Impact on Prognosis and Benefit From Adjuvant Therapy. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2020;38(29):3388-3397.

111. Leon-Castillo A, Horeweg N, Peters EEM, et al. Prognostic relevance of the molecular classification in high-grade endometrial cancer for patients staged by lymphadenectomy and without adjuvant treatment. Gynecologic oncology. 2022;164(3):577-586.

112. Kommoss S, McConechy MK, Kommoss F, et al. Final validation of the ProMisE molecular classifier for endometrial carcinoma in a large population-based case series. Ann Oncol. 2018;29(5):1180-1188.

113. Imboden S, Nastic D, Ghaderi M, et al. Implementation of the 2021 molecular ESGO/ESTRO/ESP risk groups in endometrial cancer. Gynecologic oncology. 2021;162(2):394-400.

114. McAlpine J, Leon-Castillo A, Bosse T. The rise of a novel classification system for endometrial carcinoma; integration of molecular subclasses. J Pathol. 2018;244(5):538-549.

115. Baiden-Amissah REM, Annibali D, Tuyaerts S, Amant F. Endometrial Cancer Molecular Characterization: The Key to Identifying High-Risk Patients and Defining Guidelines for Clinical Decision-Making? Cancers (Basel). 2021;13(16).

116. Billingsley CC, Cohn DE, Mutch DG, Hade EM, Goodfellow PJ. Prognostic Significance of POLE Exonuclease Domain Mutations in High-Grade Endometrioid Endometrial Cancer on Survival and Recurrence: A Subanalysis. Int J Gynecol Cancer. 2016;26(5):933-938.

117. Timmerman S, Van Rompuy AS, Van Gorp T, et al. Analysis of 108 patients with endometrial carcinoma using the PROMISE classification and additional genetic analyses for MMR-D. Gynecologic oncology. 2020.

118. Cree IA, White VA, Indave BI, Lokuhetty D. Revising the WHO classification: female genital tract tumours. Histopathology. 2020;76(1):151-156.

119. Walker JL, Piedmonte MR, Spirtos NM, et al. Laparoscopy compared with laparotomy for comprehensive surgical staging of uterine cancer: Gynecologic Oncology Group Study LAP2. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2009;27(32):5331-5336.

120. Janda M, Gebski V, Davies LC, et al. Effect of Total Laparoscopic Hysterectomy vs Total Abdominal Hysterectomy on Disease-Free Survival Among Women With Stage I Endometrial Cancer: A Randomized Clinical Trial. JAMA. 2017;317(12):1224-1233.

121. Koskas M, Jozwiak M, Fournier M, et al. Long-term oncological safety of minimally invasive surgery in high-risk endometrial cancer. Eur J Cancer. 2016;65:185-191.

122. Barlin JN, Puri I, Bristow RE. Cytoreductive surgery for advanced or recurrent endometrial cancer: a meta-analysis. Gynecologic oncology. 2010;118(1):14-18.

123. Lindfors A, Akesson A, Staf C, Sjoli P, Sundfeldt K, Dahm-Kahler P. Robotic vs Open Surgery for Endometrial Cancer in Elderly Patients: Surgical Outcome, Survival, and Cost Analysis. Int J Gynecol Cancer. 2018;28(4):692-699.

124. Giannini A, Di Donato V, Schiavi MC, May J, Panici PB, Congiu MA. Predictors of postoperative overall and severe complications after surgical treatment for endometrial cancer: The role of the fragility index. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics. 2020;148(2):174-180.
125. Mullen MM, Porcelli BP, Cripe J, et al. Modified frailty index is predictive of wound complications in obese patients undergoing gynecologic surgery via a midline vertical incision. Gynecologic oncology. 2020;157(1):287-292.
126. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-383.
127. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. J Clin Epidemiol. 1994;47(11):1245-1251.
128. Robbins JR, Gayar OH, Zaki M, Mahan M, Buekers T, Elshaikh MA. Impact of Age-Adjusted Charlson Comorbidity score on outcomes for patients with early-stage endometrial cancer. Gynecologic oncology. 2013;131(3):593-597.
129. WHO webpage: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight Accessed Dec 27, 2022.
130. Cusimano MC, Simpson AN, Dossa F, et al. Laparoscopic and robotic hysterectomy in endometrial cancer patients with obesity: a systematic review and meta-analysis of conversions and complications. Am J Obstet Gynecol. 2019;221(5):410-428 e419.
131. Leitao MM, Narain WR, Boccamazzo D, et al. Impact of Robotic Platforms on Surgical Approach and Costs in the Management of Morbidly Obese Patients with Newly Diagnosed Uterine Cancer. Ann Surg Oncol. 2016;23(7):2192-2198.
132. Bernardini MQ, Gien LT, Tipping H, Murphy J, Rosen BP. Surgical outcome of robotic surgery in morbidly obese patient with endometrial cancer compared to laparotomy. Int J Gynecol Cancer. 2012;22(1):76-81.
133. Lindfors A, Heshar H, Adok C, Sundfeldt K, Dahm-Kahler P. Long-term survival in obese patients after robotic or open surgery for endometrial cancer. Gynecologic oncology. 2020;158(3):673-680.
134. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240(2):205-213.
135. Clavien PA, Sanabria JR, Strasberg SM. Proposed classification of complications of surgery with examples of utility in cholecystectomy. Surgery. 1992;111(5):518-526.
136. Martin RC, 2nd, Brennan MF, Jaques DP. Quality of complication reporting in the surgical literature. Ann Surg. 2002;235(6):803-813.
137. Strasberg SM, Linehan DC, Hawkins WG. The accordion severity grading system of surgical complications. Ann Surg. 2009;250(2):177-186.
138. Dindo D, Demartines N, Clavien P-A. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Annals of surgery. 2004;240(2):205.
139. Leitao MM, Jr., Zhou QC, Gomez-Hidalgo NR, et al. Patient-reported outcomes after surgery for endometrial carcinoma: Prevalence of lower-extremity lymphedema after sentinel lymph node mapping versus lymphadenectomy. Gynecologic oncology. 2020;156(1):147-153.
140. Todo Y, Yamazaki H, Takeshita S, et al. Close relationship between removal of circumflex iliac nodes to distal external iliac nodes and postoperative lower-extremity lymphedema in uterine corpus malignant tumors. Gynecologic oncology. 2015;139(1):160-164.
141. Salehi S, Avall-Lundqvist E, Brandberg Y, Johansson H, Suzuki C, Falconer H. Lymphedema, serious adverse events, and imaging 1 year after comprehensive staging for endometrial cancer: results from the RASHEC trial. Int J Gynecol Cancer. 2019;29(1):86-93.
142. Onsrud M, Cvancarova M, Hellebust TP, Tropé CG, Kristensen GB, Lindemann K. Long-term outcomes after pelvic radiation for early-stage endometrial cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2013;31(31):3951-3956.
143. Creutzberg CL, Van Putten WLJ, Koper PCM, et al. Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: Multicentre randomised trial. Lancet. 2000;355(9213):1404-1411.

144. Creutzberg CL, Van Putten WLJ, Koper PC, et al. Survival after relapse in patients with endometrial cancer: Results from a randomized trial. Gynecologic oncology. 2003;89(2):201-209.

145. Poulsen HK, Jacobsen M, Bertelsen K, et al. Adjuvant radiation therapy is not necessary in the management of endometrial carcinoma stage I, low-risk cases. International Journal of Gynecological Cancer. 1996;6(1):38-43.

146. Aalders J, Abeler V, Kolstad P, Onsrud M. Postoperative external irradiation and prognostic parameters in stage I endometrial carcinoma: clinical and histopathologic study of 540 patients. Obstet Gynecol. 1980;56(4):419-427.

147. R A Nout VTHBMS, H Putter, I M Jürgenliemk-Schulz, J J Jobsen, L C H W Lutgens, E M van der Steen-Banasik, J W M Mens, A Slot, M C Stenfert Kroese, B N F M van Bunningen, A C Ansink, W L J van Putten, C L Creutzberg. Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): an open-label, non-inferiority, randomised trial. lancet. 2010.

148. Wortman BG, Creutzberg CL, Putter H, et al. Ten-year results of the PORTEC-2 trial for high-intermediate risk endometrial carcinoma: improving patient selection for adjuvant therapy. Br J Cancer. 2018;119(9):1067-1074.

149. Ortoft G, Hansen ES, Bertelsen K. Omitting adjuvant radiotherapy in endometrial cancer increases the rate of locoregional recurrences but has no effect on long-term survival: the Danish Endometrial Cancer Study. Int J Gynecol Cancer. 2013;23(8):1429-1437.

150. Maggi R, Lissoni A, Spina F, et al. Adjuvant chemotherapy vs radiotherapy in high-risk endometrial carcinoma: results of a randomised trial. Br J Cancer. 2006;95(3):266-271.

151. Susumu N, Sagae S, Udagawa Y, et al. Randomized phase III trial of pelvic radiotherapy versus cisplatin-based combined chemotherapy in patients with intermediate- and high-risk endometrial cancer: a Japanese Gynecologic Oncology Group study. Gynecologic oncology. 2008;108(1):226-233.

152. Hogberg T, Signorelli M, de Oliveira CF, et al. Sequential adjuvant chemotherapy and radiotherapy in endometrial cancer--results from two randomised studies. Eur J Cancer. 2010;46(13):2422-2431.

153. Randall ME, Filiaci VL, Muss H, et al. Randomized phase III trial of whole-abdominal irradiation versus doxorubicin and cisplatin chemotherapy in advanced endometrial carcinoma: a Gynecologic Oncology Group Study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2006;24(1):36-44.

154. Matei D, Filiaci V, Randall ME, et al. Adjuvant Chemotherapy plus Radiation for Locally Advanced Endometrial Cancer. N Engl J Med. 2019;380(24):2317-2326.

155. de Boer SM, Powell ME, Mileshkin L, et al. Adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): final results of an international, open-label, multicentre, randomised, phase 3 trial. Lancet Oncol. 2018;19(3):295-309.

156. Green AK, Feinberg J, Makker V. A Review of Immune Checkpoint Blockade Therapy in Endometrial Cancer. Am Soc Clin Oncol Educ Book. 2020;40:1-7.

157. Vizza E, Cutillo G, Bruno V, et al. Pattern of recurrence in patients with endometrial cancer: A retrospective study. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology. 2020;46(9):1697-1702.

158. Fung-Kee-Fung M, Dodge J, Elit L, et al. Follow-up after primary therapy for endometrial cancer: a systematic review. Gynecologic oncology. 2006;101(3):520-529.

159. Bendifallah S, Ouldamer L, Lavoue V, et al. Patterns of recurrence and outcomes in surgically treated women with endometrial cancer according to ESMO-ESGO-ESTRO Consensus Conference risk groups: Results from the FRANCOGYN study Group. Gynecologic oncology. 2017;144(1):107-112.

160. de Boer SM, Powell ME, Mileshkin L, et al. Adjuvant chemoradiotherapy versus radiotherapy alone in women with high-risk endometrial cancer (PORTEC-3): patterns of recurrence and post-hoc survival analysis of a randomised phase 3 trial. Lancet Oncol. 2019;20(9):1273-1285.

161. Sartori E, Pasinetti B, Carrara L, Gambino A, Odicino F, Pecorelli S. Pattern of failure and value of follow-up procedures in endometrial and cervical cancer patients. Gynecologic oncology. 2007;107(1 Suppl 1):S241-247.

162. Bendifallah S, Ilenko A, Daraï E. High risk endometrial cancer: Clues towards a revision of the therapeutic paradigm. Journal of Gynecology Obstetrics and Human Reproduction. 2019;48(10):863-871.
163. Ignatov T, Eggemann H, Costa SD, Ortmann O, Ignatov A. Endometrial cancer subtypes are associated with different patterns of recurrence. Journal of cancer research and clinical oncology. 2018;144(10):2011-2017.
164. Bristow RE, Santillan A, Zahurak ML, Gardner GJ, Giuntoli RL, 2nd, Armstrong DK. Salvage cytoreductive surgery for recurrent endometrial cancer. Gynecologic oncology. 2006;103(1):281-287.
165. Sharma AE, Moran A, Somasegar S, et al. Clinicopathologic Evaluation and Molecular Profiling of Recurrent Stage IA Endometrial Endometrioid Carcinoma: A Case-control Study. Int J Gynecol Pathol. 2023;42(1):26-34.
166. Sorbe B, Soderstrom K. Treatment of vaginal recurrences in endometrial carcinoma by high-dose-rate brachytherapy. Anticancer research. 2013;33(1):241-247.
167. van Wijk FH, van der Burg ME, Burger CW, Vergote I, van Doorn HC. Management of recurrent endometrioid endometrial carcinoma: an overview. Int J Gynecol Cancer. 2009;19(3):314-320.
168. Yoshiba T, Takei Y, Machida S, et al. Prognosis of endometrial cancer patients with and without symptoms at recurrence. The journal of obstetrics and gynaecology research. 2016;42(12):1814-1821.
169. Ackerman I, Malone S, Thomas G, Franssen E, Balogh J, Dembo A. Endometrial carcinoma--relative effectiveness of adjuvant irradiation vs therapy reserved for relapse. Gynecologic oncology. 1996;60(2):177-183.
170. Salani R, Nagel CI, Drennen E, Bristow RE. Recurrence patterns and surveillance for patients with early stage endometrial cancer. Gynecologic oncology. 2011;123(2):205-207.
171. Lee JY, Kim JH, Seo JW, et al. Detecting Asymptomatic Recurrence in Early-Stage Endometrial Cancer: The Value of Vaginal Cytology, Imaging Studies, and CA-125. Int J Gynecol Cancer. 2016;26(8):1434-1439.
172. Nikolopoulos M, Godfrey MAL, Sohrabi F, Wong M, Bhatte D, Wuntakal R. Stage one endometrioid endometrial adenocarcinoma: is there a role of traditional hospital follow-up in the detection of cancer recurrence in women after treatment? Obstet Gynecol Sci. 2021;64(6):506-516.
173. Salvesen HB, Akslen LA, Iversen T, Iversen OE. Recurrence of endometrial carcinoma and the value of routine follow up. Br J Obstet Gynaecol. 1997;104(11):1302-1307.
174. Jeppesen MM, Mogensen O, Hansen DG, Bergholdt SH, Jensen PT. How Do We Follow Up Patients With Endometrial Cancer? Curr Oncol Rep. 2019;21(7):57.
175. Coleridge S, Morrison J. Patient-initiated follow-up after treatment for low risk endometrial cancer: a prospective audit of outcomes and cost benefits. Int J Gynecol Cancer. 2020;30(8):1177-1182.
176. Jeppesen MM, Jensen PT, Gilsa Hansen D, Iachina M, Mogensen O. The nature of early-stage endometrial cancer recurrence-A national cohort study. Eur J Cancer. 2016;69:51-60.
177. Xu Y, Burmeister C, Hanna RK, Munkarah A, Elshaikh MA. Predictors of Survival After Recurrence in Women With Early-Stage Endometrial Carcinoma. Int J Gynecol Cancer. 2016;26(6):1137-1142.
178. Legge F, Restaino S, Leone L, et al. Clinical outcome of recurrent endometrial cancer: analysis of post-relapse survival by pattern of recurrence and secondary treatment. Int J Gynecol Cancer. 2020;30(2):193-200.
179. Asplund K S. Socialstyrelsens cancerrapport till regeringen - Lägesrapport 2006.
180. SQRGC styrgrupp. Årsrapport 2022.
181. Rosenberg P, Kjolhede P, Staf C, et al. Data quality in the Swedish Quality Register of Gynecologic Cancer - a Swedish Gynecologic Cancer Group (SweGCG) study. Acta Oncol. 2018;57(3):346-353.
182. Nationellt vårdprogram livmoderkroppscancer. Sweden; RCC 2012
183. McDonald ME, Bender DP. Endometrial Cancer: Obesity, Genetics, and Targeted Agents. Obstet Gynecol Clin North Am. 2019;46(1):89-105.
184. Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg. 2009;250(2):187-196.

185. Leone FP, Timmerman D, Bourne T, et al. Terms, definitions and measurements to describe the sonographic features of the endometrium and intrauterine lesions: a consensus opinion from the International Endometrial Tumor Analysis (IETA) group. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2010;35(1):103-112.

186. Nougaret S, Horta M, Sala E, et al. Endometrial Cancer MRI staging: Updated Guidelines of the European Society of Urogenital Radiology. Eur Radiol. 2019;29(2):792-805.

187. Kaplan EL, Meier P. Nonparametric Estimation from Incomplete Observations. Journal of the American Statistical Association. 1958;53(282):457-481.

188. Pavlic K, Perme MP. On comparison of net survival curves. BMC medical research methodology. 2017;17(1):79.

189. Perme MP, Stare J, Estève J. On Estimation in Relative Survival. Biometrics. 2012;68(1):113-120.

190. Scrucca L, Santucci A, Aversa F. Competing risk analysis using R: an easy guide for clinicians. Bone Marrow Transplant. 2007;40(4):381-387.

191. Koskas M, Genin AS, Graesslin O, et al. Evaluation of a method of predicting lymph node metastasis in endometrial cancer based on five pre-operative characteristics. European journal of obstetrics, gynecology, and reproductive biology. 2014;172:115-119.

192. Kilgore JE, Jackson AL, Ko EM, et al. Recurrence-free and 5-year survival following robotic-assisted surgical staging for endometrial carcinoma. Gynecologic oncology. 2013;129(1):49-53.

193. Esselen KM, Boruta DM, del Carmen M, Schorge JO, Goodman A, Growdon WB. Defining Prognostic Variables in Recurrent Endometrioid Endometrial Cancer: A 15-Year Single-Institution Review. International Journal of Gynecologic Cancer. 2011;21(6):1078-1083.

194. Fujimoto T, Nanjyo H, Fukuda J, et al. Endometrioid uterine cancer: histopathological risk factors of local and distant recurrence. Gynecologic oncology. 2009;112(2):342-347.

195. Obermair A, Manolitsas TP, Leung Y, Hammond IG, McCartney AJ. Total laparoscopic hysterectomy for endometrial cancer: patterns of recurrence and survival. Gynecologic oncology. 2004;92(3):789-793.

196. Walker JL, Piedmonte MR, Spirtos NM, et al. Recurrence and survival after random assignment to laparoscopy versus laparotomy for comprehensive surgical staging of uterine cancer: Gynecologic Oncology Group LAP2 Study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2012;30(7):695-700.

197. Feigenberg T, Cormier B, Gotlieb WH, et al. Factors associated with an increased risk of recurrence in patients diagnosed with high-grade endometrial cancer undergoing minimally invasive surgery: A study of the society of gynecologic oncology of Canada (GOC) community of practice (CoP). Gynecologic oncology. 2021;162(3):606-612.

198. Song J, Le T, Hopkins L, et al. A comparison of disease recurrence between robotic versus laparotomy approach in patients with intermediate-risk endometrial cancer. Int J Gynecol Cancer. 2020;30(2):160-166.

199. Kilic F, Unsal M, Cakir C, et al. Prognostic factors determining survival after extrapelvic recurrence in endometrioid type endometrial cancer. Taiwanese journal of obstetrics & gynecology. 2021;60(6):1023-1030.

200. Francis SR, Ager BJ, Do OA, et al. Recurrent early stage endometrial cancer: Patterns of recurrence and results of salvage therapy. Gynecologic oncology. 2019;154(1):38-44.

201. Chan JK, Kapp DS, Cheung MK, et al. The impact of the absolute number and ratio of positive lymph nodes on survival of endometrioid uterine cancer patients. Br J Cancer. 2007;97(5):605-611.

202. Ørtoft G, Høgdall C, Juhl C, Petersen LK, Hansen ES, Dueholm M. The effect of introducing pelvic lymphadenectomy on survival and recurrence rates in Danish endometrial cancer patients at high risk: a Danish Gynecological Cancer Group study. Int J Gynecol Cancer. 2019;29(1):68-76.

203. Dahm-Kahler P, Palmqvist C, Staf C, Holmberg E, Johannesson L. Centralized primary care of advanced ovarian cancer improves complete cytoreduction and survival - A population-based cohort study. Gynecologic oncology. 2016;142(2):211-216.

204. Palmqvist C, Staf C, Mateoiu C, Johansson M, Albertsson P, Dahm-Kahler P. Increased disease-free and relative survival in advanced ovarian cancer after centralized primary treatment. Gynecologic oncology. 2020;159(2):409-417.

205. Chan WS, Kong KK, Nikam YA, Merkur H. Vaginal vault dehiscence after laparoscopic hysterectomy over a nine-year period at Sydney West Advanced Pelvic Surgery Unit - our experiences and current understanding of vaginal vault dehiscence. Aust N Z J Obstet Gynaecol. 2012;52(2):121-127.
206. Drudi L, Press JZ, Lau S, et al. Vaginal vault dehiscence after robotic hysterectomy for gynecologic cancers: search for risk factors and literature review. Int J Gynecol Cancer. 2013;23(5):943-950.
207. Pin S, Mateshaytis J, Ghosh S, Batuyong E, Easaw JC. Risk factors for venous thromboembolism in endometrial cancer. Curr Oncol. 2020;27(4):198-203.
208. Jorgensen SL, Mogensen O, Wu C, et al. Nationwide Introduction of Minimally Invasive Robotic Surgery for Early-Stage Endometrial Cancer and Its Association With Severe Complications. JAMA surgery. 2019;154(6):530-538.
209. SQRGC. Klinikrapport 2022.
210. Polan RM, Rossi EC, Barber EL. Extent of lymphadenectomy and postoperative major complications among women with endometrial cancer treated with minimally invasive surgery. Am J Obstet Gynecol. 2019;220(3):263.e261-263.e268.
211. Accorsi GS, Paiva LL, Schmidt R, Vieira M, Reis R, Andrade C. Sentinel Lymph Node Mapping vs Systematic Lymphadenectomy for Endometrial Cancer: Surgical Morbidity and Lymphatic Complications. Journal of minimally invasive gynecology. 2019.
212. Geppert B, Persson J. Robotic infrarenal paraaortic and pelvic nodal staging for endometrial cancer: feasibility and lymphatic complications. Acta obstetricia et gynecologica Scandinavica. 2015;94(10):1074-1081.
213. Geppert B, Lonnerfors C, Bollino M, Persson J. Sentinel lymph node biopsy in endometrial cancer-Feasibility, safety and lymphatic complications. Gynecologic oncology. 2018;148(3):491-498.
214. Bouwman F, Smits A, Lopes A, et al. The impact of BMI on surgical complications and outcomes in endometrial cancer surgery--an institutional study and systematic review of the literature. Gynecologic oncology. 2015;139(2):369-376.
215. Gunderson CC, Java J, Moore KN, Walker JL. The impact of obesity on surgical staging, complications, and survival with uterine cancer: a Gynecologic Oncology Group LAP2 ancillary data study. Gynecologic oncology. 2014;133(1):23-27.
216. Wysham WZ, Kim KH, Roberts JM, et al. Obesity and perioperative pulmonary complications in robotic gynecologic surgery. Am J Obstet Gynecol. 2015;213(1):33 e31-33 e37.
217. Fader AN, Seamon LG, Escobar PF, et al. Minimally invasive surgery versus laparotomy in women with high grade endometrial cancer: a multi-site study performed at high volume cancer centers. Gynecologic oncology. 2012;126(2):180-185.
218. Barrie A, Freeman AH, Lyon L, et al. Classification of Postoperative Complications in Robotic-assisted Compared With Laparoscopic Hysterectomy for Endometrial Cancer. Journal of minimally invasive gynecology. 2016;23(7):1181-1188.
219. Folkhälsomyndigheten webpage, accessed on Dec 27, 2022: https://www.folkhalsomyndigheten.se/folkhalsorapportering-statistik/tolkad-rapportering/folkhalsans-utveckling/resultat/levnadsvanor/ tobaksrokning-daglig/.
220. Eriksson LSE, Epstein E, Testa AC, et al. Ultrasound-based risk model for preoperative prediction of lymph-node metastases in women with endometrial cancer: model-development study. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2020;56(3):443-452.
221. Fischerova D, Fruhauf F, Zikan M, et al. Factors affecting sonographic preoperative local staging of endometrial cancer. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2014;43(5):575-585.
222. Rothman KJ. Epidemiology, An introduction. 2 ed2011.
223. Dholakia J, Llamocca E, Quick A, Salani R, Felix AS. Guideline-concordant treatment is associated with improved survival among women with non-endometrioid endometrial cancer. Gynecologic oncology. 2020;157(3):716-722.
224. Ortoft G, Hogdall C, Juhl C, Petersen LK, Hansen ES, Dueholm M. Location of recurrences in high-risk stage Iendometrial cancer patients not given postoperative radiotherapy: A Danish gynecological cancer group study. Int J Gynecol Cancer. 2019;29(3):497-504.

225. Siegenthaler F, Lindemann K, Epstein E, et al. Time to first recurrence, pattern of recurrence, and survival after recurrence in endometrial cancer according to the molecular classification. Gynecologic oncology. 2022;165(2):230-238.
226. Backes FJ, Haag J, Cosgrove CM, Suarez A, Cohn DE, Goodfellow PJ. Mismatch repair deficiency identifies patients with high-intermediate-risk (HIR) endometrioid endometrial cancer at the highest risk of recurrence: A prognostic biomarker. Cancer. 2019;125(3):398-405.
227. How J, Gauthier C, Abitbol J, et al. Impact of sentinel lymph node mapping on recurrence patterns in endometrial cancer. Gynecologic oncology. 2017;144(3):503-509.
228. Murakami K, Kotani Y, Suzuki A, et al. Superparamagnetic iron oxide as a tracer for sentinel lymph node detection in uterine cancer: a pilot study. Sci Rep. 2020;10(1):7945.
229. Rockall AG, Sohaib SA, Harisinghani MG, et al. Diagnostic performance of nanoparticle-enhanced magnetic resonance imaging in the diagnosis of lymph node metastases in patients with endometrial and cervical cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2005;23(12):2813-2821.

Mätprotokoll Pre-Operativ Diagnostik av EndometrieCancer (PODEC)

Patientens namn: .....

Person-nr: .....

BMI: .....

Apparatnamn: .....

Myometrieinvasion: <50 % ☐ ≥50 % ☐ ej bedömbart ☐

Cervixstromainvasion: nej ☐ ja ☐ ej bedömbart ☐

Serosagenombrott: nej ☐ ja ☐ ej bedömbart ☐

Annat relevant fynd (myom, adenomyos, extrauterin expansivitet, ascites etc):

.....

Artefakter eller andra faktorer som påverkat bildkvaliteten/bedömbarheten:

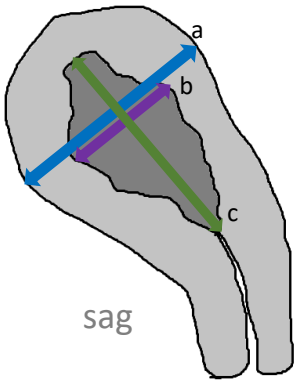
nej ☐ ja ☐ .....

Mått (mm):

a) Max uterin anteroposterior .....

b) Max tumör anteroposterior (eller endometrietjocklek vid avsaknad av synlig tumör) .....

c) Max tumör fundocervicalt ..... **d) max tumör transaxialt** .....



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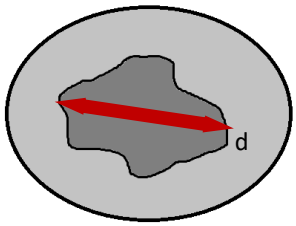

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Bedömare: ..... Ort, datum: .....

PODEC är en multicenterstudie i Västra Sjukvårdsregionen med huvudsyftet att jämföra specialiserat transvaginalt ultraljud med MRT för preoperativ bedömning av infiltrationsdjup av endometriecancer. Deltagande specialister i gynekologisk tumörkirurgi inkluderar efter informerat samtycke fortlöpande patienter med endometriecancer av lågrisktyp (på SU-S även högrisktyp) enligt PAD som remitterats till dem och bedöms operabla om följande **exklusionskriterier** inte föreligger:

-Ungdom (< 18 år)

-Graviditet

-Sedvanliga kontraindikationer för MRT, såsom pacemaker, vissa metallimplantat, svår klaustrofobi (se lokal kontrollista inför MRT-undersökning för mer detaljer)

-Överkänslighet mot Gadoliniumkontrastmedel

-Gravt nedsatt njurfunktion (GFR < 30)

-Kraftig övervikt (BMI > 45)

-Oförmåga att förstå svenska i tal och skrift

Ultraljud- respektive MRT-bedömningarna jämförs med golden standard i form av postoperativ patologisk analys med PAD-utlåtande på respektive enhet. Patolog med gynekologisk cancer som specialitet på SU-S eftergranskar preparaten i möjligaste mån och fyller i mätprotokoll med måttangivelser som motsvarar de för ultraljudsbedömningen.

OBS! Om MRT-undersökningen har hunnit genomföras före ultraljudet är det, för att att undvika bias, av yttersta vikt att bilder eller utlåtande inte studeras före ultraljudsundersökningen. När väl mätprotokollet är färdigställt är det tillåtet att ta del av MRT-informationen (bilder, eller granskningsutlåtande från SU-S), men då förstås utan att korrigera det ifyllda protokollet.

PS! Glöm inte att skriva remiss med klinisk info för *MRT endometriecancer (PODEC-studien)* som kan göras på deltagande enhet (SU-S, NÄL, SÄS Borås, SKAS-KSS resp Varbergs sjukhus eller angränsande sjukhus med MRT-enhet), bilderna ska länkas till SU-S. I oklara fall som bedöms ha betydelse för den fortsatta handläggningen kan granskningsremiss till Röntgen SU-S (Henrik Leonhardt) skrivas. Lokal radiolog behöver alltså inte bedöma undersökningen och utlåtandet kan skrivas ”PODEC-studien”. Markera också den postoperativa PAD-remissen med *PODEC-studien*.

Ifyllt mätprotokoll skickas med samtyckesformuläret i förslutet kuvert till:

Kliniska Prövningsenheten (KP-nr KP0259)
Radiologi
Bruna stråket 11 B
SU/Sahlgrenska
413 45 Göteborg