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Robotic-assisted laparoscopic hysterectomy for women with endometrial cancer - complications, women's experiences, quality of life and a health economic evaluation.

PhD thesis

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Indhold

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“Far better an approximate answer to the right question, which is often vague, than an exact answer to the wrong question, which can always be made precise.”
John Tukey (Tukey, 1962)

ABBREVIATIONS

ABC: Activity-based costing

ACH: Atypical complex hyperplasia

ARR: Absolute Risk Reduction

BMI: Body Mass index

BSO: Bilateral salpingo-oophorectomy

CI: Confidence interval

DKK: Danish Kroner

DRG: Diagnosis-related Group

FDA: Food and Drug Administration

GP: General practioner

HRQoL: Health-Related Quality of life

LOS: Length of stay

MIS: Minimally Invasive Surgery

OR: Odds Ratio

PACU: Post-anaesthetic Care Unit

PLA: Pelvic Lymphadenectomy

PONV: Post-operative nausea and vomiting

PROMs: Patient-reported outcome measures

RALH: Robotic-assisted laparoscopic hysterectomy

RCT: Randomised controlled trial

TAH: Total abdominal hysterectomy

Qol: Quality of life

SUMMARY

This thesis contains four studies all focusing on women with endometrial cancer undergoing robotic-assisted laparoscopic hysterectomy (RALH). Women with endometrial cancer are typically elderly with comorbidities. RALH is a relatively new treatment option which has been introduced and adopted over the last decade without randomised controlled trials (RCTs) to prove superiority over other surgical alternatives. The purpose of the thesis was to explore and describe patient and health economic outcomes of RALH for women with endometrial cancer using different research approaches.

The first study was a retrospective descriptive cohort study with 235 women. The aim was to explore types and incidence of postoperative complications within 12 months after RALH reported with the Clavien-Dindo scale. We found that 6 % had severe complications and that women with lymphadenectomy did not have an increased rate of complications. Urinary tract and port site infections were the most frequent complications.

The second study was a qualitative interview study where we explored the experience of undergoing RALH. Using content analysis, we analysed semi-structured interviews with 12 women who had undergone RALH on average 12 weeks earlier. The women were positive towards the robotic approach and felt recovered shortly after. They expressed uncertainty with the normal course of bleeding and bowel movement postoperatively as well as with the new anatomy.

The third study was an economic evaluation; an activity based costing study including 360 women comparing total abdominal hysterectomy (TAH) to RALH. This study showed that for women with endometrial cancer, RALH was cheaper compared to TAH, mainly due to fewer complications and shorter length of stay (LOS) that counterbalanced the higher robotic expenses. When including all cost drivers the analysis showed that the RALH procedure was more than 9.000 Danish kroner (DKK) cheaper than the TAH. Increased age and Type 2 diabetes appeared to increase costs.

The fourth study was a prospective cohort study of 139 women who were followed 4 months after surgery with the aim to assess short term changes in health-related quality of life (HRQoL), symptoms and function after RALH. Both a general and an illness specific HRQoL questionnaire were used. The preoperative baseline measurement was compared with measurements at 1 and 5 weeks and 4 months postoperatively. The women also self- reported their level of activity once a week for the first 5 weeks after surgery. We found that HRQoL was back to baseline level at 5 weeks postoperatively for the majority of women. Fatigue, constipation, gastrointestinal

symptoms, pain, appetite and change of taste were negatively affected short term. At five weeks the mean level of physical activity resumed was 84 %.

Together, the studies indicate that RALH is a well-tolerated surgical treatment for women with endometrial cancer, and postoperative complications appear fewer and less severe compared to previous open surgery. This points towards RALH being clinically and economically efficient. The women experienced that RALH was easy to overcome and they felt recovered shortly after. However, they expressed uncertainty about the normal postoperative cause and reported changes in functions and symptoms short term after surgery. These changes should be addressed in the preoperative information and at the postoperative follow-up.

It is difficult imagining a RCT of robotic-assisted laparoscopic hysterectomy being conducted in the future due to reluctance towards randomisation to open surgery. However, it would be advisable continuously to monitor relevant surgical and patient-reported outcomes as indications for robotic surgery may alter, experiences may develop and further technical advances may change robotic surgery for women with endometrial cancer in future.

RESUMÉ

Denne Ph.d.-afhandling omhandler fire studier, som alle fokuserer på kvinder med corpus cancer, som gennemgår Robot Assisteret Laparoskopisk Hysterektomi (RALH). Kvinder med corpus cancer er typisk ældre med komorbiditet. RALH er et relativ nyt behandlings tilbud, der blev introduceret og hastigt implementeret over det sidste årti uden evidens fra randomiserede kliniske undersøgelser (RCT), der påviser, at RALH udgør et bedre behandlingstilbud i forhold til andre kirurgiske alternativer. Formålet med denne afhandling er at undersøge og beskrive patientudbyttet og det sundhedsøkonomiske udbytte af RALH for kvinder med corpus cancer ved hjælp af forskellige forskningsmetoder.

Det første studie var et retrospektivt deskriptivt kohorte studie med 235 kvinder. Formålet var at undersøge typer og incidens af postoperative komplikationer målt indenfor 12 måneder efter RALH ved Clavien-Dindo skalaen. Vi fandt, at 6 % udviklede svære komplikationer og at kvinder. som fik foretaget lymfadenektomi, ikke havde en højere frekvens af komplikationer. Urinvejsinfektioner og infektioner i porthuller var de hyppigste forekommende komplikationer.

Det andet studie var et kvalitativt interview studie, hvor vi undersøgte oplevelsen af at gennemgå RALH. Gennem indholdsanalyse analyserede vi semistrukturerede interviews med 12 kvinder, som havde gennemgået RALH i gennemsnit 12 uger tidligere. Kvinderne var positive omkring robot tilgangen og oplevede, at de kom sig hurtigt bagefter. De udtrykte usikkerhed om, hvordan det normale postoperative forløb var i forbindelse med blødning og mavetarmfunktion og var usikre på den forandrede anatomi.

Det tredje studie var en økonomisk evaluering, et ”Activity – based costing” studie, der inkluderede 360 kvinder, hvor total abdominal hysterektomi (TAH) blev sammenlignet med RALH. Studiet viste, at for kvinder med corpus cancer var RALH billigere end TAH, mest grundet færre komplikationer og kortere indlæggelsestid, som modsvarede de højere udgifter til selve robotkirurgien. Når man inkluderede alle ressourceforbrugende aktiviteter (cost drivers) viste analysen, at RALH var mere end 9.000 DKK billigere end TAH. Højere alder og type 2 diabetes kunne tilsyneladende øge udgifterne.

Det fjerde studie var et prospektivt kohorte studie med 139 kvinder, som blev fulgt i 4 måneder efter kirurgi. Formålet var, at undersøge de umiddelbare forandringer i sundhedsrelateret livskvalitet, symptomer og funktioner efter RALH. Både et generisk og et sygdomsspecifikt sundhedsrelateret livskvalitetsspørgeskema blev anvendt. Måling før operationen blev sammenlignet med målinger efter en uge, fem uger og 4 måneder postoperativt. Kvinderne selv-rapporterede også deres aktivitetsniveau én gang om ugen de første 5 uger efter operationen. Vi

fandt for hovedparten af kvinderne, at sundhedsrelateret livskvalitet var på samme niveau som før operationen, 5 uger efter kirurgien. Træthed, forstoppelse, mavetarmfunktion, smerter, appetit og forandret smagsoplevelse var negativt påvirket på kort sigt. Efter fem uger var det gennemsnitlige niveau for den genvundne fysiske aktivitet på 84 %.

Tilsammen indikerer studierne, at RALH er en kirurgisk behandling, der er veltolereret blandt kvinder med corpus cancer og har tilsyneladende få og mindre alvorlige komplikationer i sammenligning med tidligere åben kirurgi. Dette peger på at RALH er en klinisk og økonomisk effektiv behandling. Kvinderne oplevede at, at kirurgien var let at komme sig over og de følte sig raske kort tid efter. Ikke desto mindre var kvinderne usikre på det normale postoperative forløb og rapporterede forandringer i funktioner og symptomer på kort sigt efter operationen. Disse forandringer bør inddrages i præoperativ information og i den postoperative opfølgning.

Det er det vanskeligt, at forestille sig at et RCT med RALH vil blive udført i fremtiden på grund af modviljen til at randomisere til åben kirurgi. Ikke desto mindre vil det være tilrådeligt kontinuerligt at overvåge det kirurgiske og patientrapporterede udbytte idet indikationer for robotkirurgi kan ændres, erfaringer kan udbygges og flere teknologiske fremskridt kan forandre robotkirurgien for kvinder med corpus cancer i fremtiden.

LISTS OF PAPERS

The PhD thesis is summarised in the following synopsis. The Ph.D. is based on the following four studies:

Paper I

Robotic-assisted laparoscopic hysterectomy seems safe in women with early-stage endometrial cancer

Status: Published in Dan Med J. 2015 Aug;62(8):A5109.

Authors: **Herling SF**; Havemann MC, Palle C, Møller AM; Thomsen T

Paper II

The experience of Robotic-assisted laparoscopic hysterectomy for women treated for early-stage endometrial cancer – A qualitative study

Status: Published in Cancer Nurs. 2015 Apr 15. [Epub ahead of print]

Authors: **Herling SF**; Palle C; Møller AM, Thomsen T.

Paper III

Cost analysis of robotic-assisted laparoscopic hysterectomy versus total abdominal hysterectomy for women with endometrial cancer and atypical complex hyperplasia.

Status: Published in Acta Obstet Gynecol Scand. 2015 Nov 17. doi: 10.1111/aogs.12820 [Epub ahead of print]

Authors: **Herling SF**, Palle C, Møller AM; Thomsen T, Sørensen J.

Paper IV

Health-related quality of life and pain after robotic-assisted laparoscopic hysterectomy for women with endometrial cancer - A prospective cohort study

Status: Published in Gynecol Oncol. 2015 Nov 2. pii: S0090-8258(15)30171-2. doi: 10.1016/j.ygyno.2015.10.024. [Epub ahead of print]

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INTRODUCTION

Robotic surgery has been implemented without prior randomised controlled trials

Technological innovations are major drivers of rising costs in the health care system and there is an on-going intense debate concerning the pros and cons of expensive robotic surgery, specifically given the increasing economic constraints within the health care system (Barbash GI & Glied SA, 2010; Weissman & Zinner, 2013). Significant commercial interest in robotics makes it controversial and reports of outcomes from robotics tend to come from proponents of the robotic approach (Liu et al., 2014). Nevertheless robotic surgery has seen enormous growth over the past decade in several fields, including gynaecology (Visco & Advincular, 2008). An issue in the debate is the lack of high-grade evidence supporting the robotic approach. “Robotic hysterectomy is being adopted faster than the literature is supporting, and that’s one of the big problems.” Says Jason Wright, MD, of Columbia University College of Physicians and Surgeons (Kirkner, 2014).

This thesis contributes evidence for clinical and patient-reported outcomes following RALH. The aim is to evaluate robotic surgery for women with endometrial cancer given that it has de facto been implemented without RCTs to prove superiority.

The course of endometrial cancer

Endometrial cancer is the most common cancer in the female genital tract in North America and Europe (Amant et al., 2005). The incidence of endometrial cancer has regional differences. In North America it exceeds 20 per 100.000 women and in Europe the incidence is between 11 and 14 per 100.000 women (Sankaranarayanan & Ferlay, 2006). Approximately 74.000 women die every year of endometrial cancer world-wide (Le Gallo & Bell, 2014) with 9.000 of them being European women (Amant et al., 2005). In Denmark, there are approximately 750 cases annually and the lifetime risk for Danish women is 2 % (Danish Health and Medicines Authority, 2012).

Endometrial cancer is typically diagnosed in women in their sixties or seventies (Frédéric Amant, Mirza, & Creutzberg, 2012). The first symptom is often postmenopausal bleeding leading the women to seek medical attention (May & Bryant, 2010). This presenting symptom early in the course explains why most women are diagnosed in early stages (Amant et al., 2005). Consequently, surgical intervention is curative in most cases, and contributes to an overall

favourable prognosis for endometrial cancer. The 5-year survival rate is close to 90 %. However, the prognosis is less favourable in cases with advanced disease (O'Hara & Bell, 2012).

Long-lasting unopposed oestrogen exposure leads to endometrial hyperplasia, which increases the risk of developing atypical hyperplasia and eventually endometrial cancer (Amant et al., 2005). Approximately 45 % of women with atypical complex hyperplasia in endometrial biopsy do actually have an early endometrial cancer at final histology after hysterectomy - thus the treatment regime is identical for the two conditions (Pennant, Manek, & Kehoe, 2008).

The exact cause of endometrial cancer is unknown, but several risk factors have been identified. Obesity, nulliparity, early menarche, late menopause and unopposed oestrogen therapy in postmenopausal women are risk factors (O'Hara & Bell, 2012). Factors such as sedentary lifestyle and obesity have also been associated with the increasing incidence of endometrial cancer in high income countries over the last years (Amant et al., 2012). As high age is a risk factor, increased life expectancy is presumed to contribute to a rise in the incidence of endometrial cancer in the future (Amant et al., 2005).

Endometrial cancer can spread to the surrounding tissue, most often by infiltrating the myometrium, the cervix or the regional lymph nodes (May & Bryant, 2010). Lymph node metastases are diagnosed in approximately 10 % of early stages of endometrial cancer (Creasman et al, 1987; May & Bryant, 2010)

Advances in treatment of endometrial cancer

The principal treatment for endometrial cancer is surgical: total hysterectomy and bilateral salpingo-oophorectomy (BSO) (Amant et al., 2005; Burke et al., 2014; May & Bryant, 2010; Saso, Chatterjee, & Georgiou, 2011; Wright, Barrena Medel, Sehouli, Fujiwara, & Herzog, 2012). The Danish guidelines recommend pelvic lymphadenectomy (PLA) in cases with more than 50 % myoinvasion or high risk histology (Danish Health and Medicines Authority, 2012; Mirza, Jørgensen, Larsen, & Kiær, 2009). Additionally, para-aortic lymphadenectomy and omentectomy may be performed in selected cases (Saso et al., 2011). Lymphadenectomy provides useful prognostic information (Saso et al., 2011) but is associated with substantial short and long term morbidity. Furthermore lymphadenectomy constitutes a risk of developing lymphedema (May & Bryant, 2010).

Traditionally, TAH for endometrial cancer has been performed by laparotomy by transverse suprapubic or midline incision. In 1988 the first laparoscopic hysterectomy was

performed using fine instruments inserted through small incisions in the abdominal wall. Women were given the advantage of minimally invasive surgery (MIS) with less painful incision, shorter hospital stay and earlier recovery besides a lower rate of infection and ileus (Reich, 2007). However, overall, gynaecologic oncologists were reluctant to adopt the laparoscopic approach. Conventional laparoscopy was criticised for lacking depth perception, two-dimensional optics, camera instability, having limited range of motion, a steep learning curve for surgeons (Sinno & Fader, 2014) and prolonged operating times (Gehrig et al., 2008). Furthermore, in gynaecologic oncology, challenges related to obesity and comorbidities increased the reluctance towards using conventional laparoscopy (Backes & Fowler, 2014; Seamon, Bryant, Rheaume, & Kimball, 2009).

Robotic surgery in gynaecologic oncology

In 2005 the Food and Drug Administration (FDA) approved robotic-assisted surgery for gynaecology in USA. The robotic approach was a new type of laparoscopic surgery, allowing the surgeon to conduct the operation from a computer console situated beside the patient in the operating room (Liu et al., 2014). Originally the system was invented to perform tele-surgery for wounded soldiers in battlefield operating rooms where the surgeon was situated away from the warzone for the safety of the surgeon. The robotic approach proved technically possible, but problems with telecommunication made the technology unsuitable for military use (Holloway, Patel, Ahmad, 2009). Subsequently, the system was made available commercially and today patients can be treated with the da Vinci® System (Intuitive Surgical Systems, Inc., Sunnyvale, CA). The da Vinci System is at present the only FDA approved system on the market (Liu et al., 2014). It has three major components: the vision system, the surgeon console, and the patient-side cart. After establishing pneumoperitoneum, placing the abdominal laparoscopic ports, and "docking" the robot, the surgeon sits at the console and views the pelvis through a three-dimensional, high-definition vision system. The surgeon uses instruments that mimic the movement of the human hand and wrist (Holloway et al., 2009) and the system filters tremor of the hand (Sinno & Fader, 2014). Positioning during hysterectomy is a steep (30º) Trendelenburg position.

Gynaecologic oncologists have been positive towards the improved visualisation, possibilities for manipulation, and improved ergonomics and the shorter learning curve (Backes & Fowler, 2014). Drawbacks of the robotic approach are the high costs of acquisition and maintenance of the equipment and lack of tactile feedback (Sinno & Fader, 2014). Despite these drawbacks, the robotic-approach has steadily been introduced across the world (Conrad et al., 2015; Smorgick et

al., 2014; Wasson & Hoffman, 2015). By the end of 2013, 2900 robots have been installed worldwide, 375 in Europe and 14 in Denmark (Personal communication with sales representative from Intuitive Surgical January 28. 2014). Hysterectomy for endometrial cancer is the most frequent robotic procedure in gynaecologic oncological surgery (Mendivil, Holloway, & Boggess, 2009). Over the last decade total abdominal hysterectomy has been replaced by RALH and robotics is viewed as a way of facilitating less invasive hysterectomy (Visco & Advincular, 2008).

The Robotic Centre, Herlev and Gentofte Hospital, University of Copenhagen

The department of gynaecology is one of two Gynaecologic Oncologic centres in the Capital Region treating women with endometrial cancer. Since 2009, when the first RALH was performed at Herlev and Gentofte Hospital, University of Copenhagen, approximately 1000 robotic hysterectomies have been performed. Four trained gynaecologists performed 200 robotic-assisted hysterectomies annually; of these, approximately 120-130 were on the indication of endometrial cancer or ACH (Figure 1). Today RALH is the standard treatment here. In 2011 the Robotic Centre Herlev and Gentofte Hospital, University of Copenhagen, was established. The Centre is a collaboration between the department of Urology, Gastroenterology and Gynaecology who all use the three available surgical robots.

Figure 1. Robotic-assisted laparoscopic hysterectomy performed at Herlev and Gentofte Hospital, University of Copenhagen.

Standard care for women with endometrial cancer

Danish guidelines recommend (Danish Health and Medicines Authority, 2012, 2015b) that women suspected of endometrial cancer are referred to highly specialised gynaecological departments. The Gynaecological Department at Herlev and Gentofte Hospital, University of Copenhagen is a highly specialised gynaecologic department for treating endometrial cancer. All participants in studies I-IV were recruited from this department.

The women were diagnosed with endometrial carcinoma based on endometrial biopsy or curettage complemented by transvaginal ultrasound. In addition, the women were offered a MR scan to identify risk factors such as deep myometrial invasion and lymph node involvement. In the Gynaecological Department at Herlev and Gentofte Hospital, University of Copenhagen, RALH has been the standard surgical approach for early stage endometrial cancer since 2009. In case of dissemination the patient was treated by laparotomy or referred to the oncologist for chemoradiation. Only women in expected stage I were included in this thesis.

Patients undergoing RALH, followed a fast-track care pathway (Kehlet & Dahl, 2003) organised to focus on the clinical tenets: analgesia, enforced mobilisation, thrombosis-prophylaxis and care principles including the provision of extensive preoperative information, and, care principles as functional discharge criteria.

The included women were admitted to the ward on the day of surgery. RALH was performed in general anaesthesia with the women positioned in steep Trendelenburg position. Prior to this positioning, pneumoperitoneum was established with carbon dioxide insufflation. For the RALH procedure a four arm da Vinci S or da Vinci Si robot (da Vinci® Surgical System, Intuitive Surgical Inc, CA, USA) was used. The trocars were positioned routinely for pelvic surgery and monopolar scissors; bipolar grasper, grasper and needle driver were used. No uterine manipulator was used. The uterus was removed through the vagina and the vaginal cuff closed continuously using an absorbable suture. Pelvic lymphadenectomy (PLA) was performed when more than 50% myometrial invasion (MI) was present or when indicated by high risk histology. Infracolic omentectomy (OM) was performed in cases of serous or clear cell carcinoma. The women received a single dose of prophylactic antibiotics at the beginning of surgery and thrombosis prophylaxis was given by low molecular Heparin and anti-thrombotic stockings during the entire hospital stay. After surgery, the women were monitored in the Post-anaesthetic Care Unit (PACU) until adequate pain management and stable vital signs were ensured. The women typically returned to the

department of gynaecology during the afternoon. Upon returning to the department, the clinical tenets of the fast-track pathway were enforced.

The following day the surgeon informed women of the macroscopic findings and discharge was planned according to the condition of the patient. Approximately 7 days after surgery, the women attended the outpatient clinic where they were informed of the final histology, indication of adjuvant therapy and relevant follow-up. Women with endometrial cancer were followed in the outpatient clinic for a total of 3 years after discharge during the period in which these studies were undertaken. Women referred to adjuvant therapy were only included in retrospective studies (Paper I, III.)

BACKGROUND AND RELATED RESEARCH

The regulation of surgical devices by health authorities

Regulations for introducing new surgical devices and practices differ from those used for introducing new medical drugs. In the USA, the FDA does not regulate the practice of medicine. Manufacturers, physicians, and health care facilities are responsible for the implementation of new devices or practices (Food and Drug Aministration, 2015).

Similarly, in Denmark, the Danish Health and Medicines Authority supervises the safety of medical devices. Medical devices do not require authorisation from the Danish Health and Medicines Authority before they are commercialised (Danish Health and Medicines Authority, 2015a). When health authorities are not required to regulate new practices, regulation is handled at the local institutional level and early adopters of new practices are required to document the outcomes (Strong et al., 2014).

Laparoscopic hysterectomy versus laparotomy for women with endometrial cancer

There is a lack of high-quality evidence for the superiority of RALH over conventional laparoscopic surgery for women with endometrial cancer (Liu et al., 2014). The LAP 2 study from 2009, a RCT, provides evidence from a related field. The LAP 2 study was a large RCT (n= 2616) reporting that laparoscopic surgical staging was associated with fewer postoperative complications and reduced LOS compared to the standard laparotomy approach for early stage endometrial cancer (Walker et al., 2009). High body mass index (BMI) was identified as a risk factor for conversion to laparotomy (Walker et al., 2009). Previously, in a non-randomized trial, Gehrig and colleagues found that the robotic approach led to a lower rate of conversion in comparison to laparoscopy (Gehrig et al., 2008). The robotic approach seems to be superior in providing MIS to very obese women. An RCT assessing quality of life (QoL) in women with stage 1 endometrial cancer (n= 332) showed that QoL during recovery was significantly better in both the early and late postoperative phases after laparoscopy compared to TAH (Janda et al., 2010). A Cochrane review summarising 8 RCTs comparing laparoscopy to laparotomy for early stage endometrial cancer concluded that laparoscopy was associated with similar overall and disease-free survival and with reduced blood loss and hospital stay; however there was no significant difference in severe post-operative morbidity between the two approaches (Galaal & Bryant, 2012).

RALH versus conventional laparoscopy for benign cases

A related research area in gynaecology is the comparison of robotic surgery to laparoscopic surgery for benign diseases. A Cochrane review including 6 RCTs recently concluded, based on low-quality evidence, that complication rates for robotics might be similar to those for conventional laparoscopy. Further, the review concluded, based on moderate-quality evidence, that the duration of robotic surgery was longer and LOS shorter (Liu et al., 2014). Surgeon and patient preferences combined with evidence from RCTs in related fields (i.e. conventional laparoscopic hysterectomy for endometrial cancer and RALH for benign diagnoses), and from observational studies drive current surgical practice for treating endometrial cancer (Ramirez et al, 2012).

Non-randomised trials of RALH for endometrial cancer

Observational studies, mostly retrospective, constitute the major body of evidence from the last decade concerning the surgical treatment of women with endometrial cancer by RALH. A recent review examined 8 non-randomised studies comparing RALH with open surgery and found that patients undergoing robotic surgery consistently had shorter LOS and less estimated blood loss (Gala et al., 2014). When comparing robotic surgery to conventional laparoscopy, patients undergoing RALH again had shorter LOS, less blood loss, less postoperative pain and a faster return to normal activity level. The duration of surgery was however unclear i.e. the same or less for conventional laparoscopy (Gala et al., 2014).

Limitations of observational studies include selection bias, information bias, and confounding (Sedgwick, 2014). Strengths are that observational studies can be relevant where outcomes are rare (Grimes & Schulz, 2002b), they require less time and expenses, thus offering more opportunity for practice-based research, (Hartung & Touchette, 2009), and, potentially they have higher external validity (Grimes & Schulz, 2002a).

Triangulation of qualitative and quantitative studies can be an alternative to conducting RCTs (Bonell et al., 2011). This thesis therefore examined RALH using both quantitative and qualitative methods as well as clinical and patient-reported outcomes.

Postoperative complications and care after robotic surgery in general

Complication rates for robotic surgery are hypothesized to be similar to laparoscopic procedures. Robotic surgery differs from laparoscopic surgery in a better visual perception of depth, improved dexterity and camera stability. However, specific features of robotic surgery may influence the complication rates. Specific robotic complications may be caused by strong lateral movements of the robotic arms, lack of tactile feedback including movement of instruments outside the visual field, constant grip force of instruments, and a risk of overestimating distance due to the magnification of the visual field (Lönnerfors, Reynisson, Geppert, & Persson, 2015). Complications after surgery are not uncommon (infection, intraoperative bleeding and lesion of neighbouring organs), however patients and clinicians must be aware that complications after robotic surgery may occur at a much later date (Lönnerfors et al., 2015).

Postoperatively, patients undergoing robotic-assisted surgery need to be treated according to the same care principles as those undergoing similar non-robotic minimally invasive procedures (Francis & Winfield, 2006). However, similar to other minimally invasive approaches robotic surgery may result in a shorter LOS compared to open surgery. Shorter LOS can compromise time for " in hospital"- information, patient education and care (Brenner, Salathiel, Macey, & Krenzer, 2011; Francis & Winfield, 2006)**.**

Therefore postoperative care after robotic surgery should employ all the general principles of surgical nursing addressing pain, post-operative nausea and vomiting (PONV), immobilisation, bleeding and impaired urinary or gastrointestinal functioning as well as psycho-social reactions to surgery in due time.

SOME OF THE GAPS IN EVIDENCE

Postoperative complications measured by the Clavien-Dindo Scale

With the rapid implementation of RALH worldwide, and in lieu of the lack of high quality evidence for the superiority of RALH, postoperative complications are important to monitor continuously. Furthermore, the indication for robotic surgery may gradually widen to include more obese women and women with more comorbidity, thus increasing the risk of complications. Surgical complications are often claimed as the prime reason for changing patient treatment (Martin, Brennan, & Jaques, 2002). For women undergoing RALH, it is imperative to assess the risk of postoperative complications in relation to surgical cancer-treatment. Incomplete patient records, multiple sites of postoperative care, and concerns with public disclosure of data can hinder accurate monitoring of the postoperative course (Martin et al., 2002).

Accurate assessment of postoperative complications is challenging without standardized definitions. The Clavien-Dindo classification system for complications (Dindo, Demartines, & Clavien, 2004) (see appendix 1) has within recent years become increasingly recognized as a meaningful tool for assessing postoperative complications, also in gynaecology (Iyer et al., 2015; Seror et al., 2014; Wechter et al., 2014; Yim, Kim, & Nam, 2015; Zeng et al., 2015). The classification grades the severity of postoperative complications and enables clear differentiation between complications, treatment failures, and sequelae (Seror et al., 2014). It is well-known that complications can be poorly reported in patient records (Dindo et al., 2004). However, treatment interventions for complications are more likely to be documented thus making the Clavien-Dindo scale relevant for retrospective analysis. The use of the Clavien-Dindo scale replaces the disputable terms' "*major and minor complications*" and enables assessment of the clinical impact of a complication (Wechter et al., 2014).

With the introduction of RALH as a successor of TAH for early stage endometrial cancer, a reduced frequency of postoperative complications was anticipated. At the time of introduction, there was limited knowledge of the specific differences in complications between the two surgical modes and differences in operative outcomes. Since then, a number of observational studies have indeed reported reduced rates of postoperative complications after RALH compared to TAH (Boggess et al., 2008; ElSahwi et al., 2012; Bell MC, Torgerson J; Seshadri-Kreaden U, Suttle AW, 2008; Veljovich et al., 2008). However, these studies used different definitions of postoperative complications making comparison across settings and populations difficult.

The role of lymph node dissection in endometrial cancer remains controversial. Theoretically, lymphadenectomy may help identify patients with metastatic spread, who can benefit from adjuvant therapy and lymphadenectomy may eradicate metastatic disease (Bogani et al., 2014). However, the procedure can be associated with not only intraoperative and postoperative complications but also postoperative sequelae such as lymphedema. Several studies have found that lymph node dissection significantly increases complication rates (Dowdy et al., 2012; Kitchener, Swart, Qian, Amos, & Parmar, 2009; May & Bryant, 2010). The minimally invasive approach might reduce this morbidity (Bogani et al., 2014), but again it is unclear to what extent this translates to RALH.

Health economics

Investment in robots for robotic surgery and expenses for maintenance are substantial - between $1-2.3 million and annual service contracts cost between $100 000-170 000 (Xie, 2015). The cost is influenced by the monopoly market structure with only one manufacturer marketing robotic surgical equipment (Iavazzo, Papadopoulou, & Gkegkes, 2014). Applications of robotic-assisted surgery are additionally influenced by patients' and surgeons' preferences (Liu et al., 2014; Weissman & Zinner, 2013). In addition to the quality of patient outcomes, the cost of providing robotic-assisted surgery should also be taken into account. As it remains unclear to what extent the present robotic procedure has improved patient outcomes in comparison to the previous standard surgical treatment (TAH), the question is whether the additional cost is justified by superior patient outcomes. The efficiency in resource utilisation of RALH versus TAH can be compared by analysing the difference in resource and cost spending between the two surgical modes.

In the Society of Gynaecologic Oncology consensus statement it is recommended that cost analyses cover both direct and indirect costs and preferably both operating theatre supplies, equipment, operating and post- anaesthetic care unit (PACU) time, physicians' salaries, hospital room and board and laboratory, radiology, and pharmacy costs (Ramirez et al., 2012).

Women's experiences

Focusing research solely on quantifiable outcomes carries a risk of ignoring factors and aspects that are significant to patients (Sofaer, 1999). Qualitative research is increasingly used to understand what patients attribute to their experiences and to explore unquantifiable impacts of

treatment. In this line of research, the objective is to explore what people say in as much detail as possible, and uncover unknown areas or ideas (Britten, 1995). Studies focusing on the experience of hysterectomy are few. A qualitative study of women recovering after abdominal hysterectomy for benign conditions reported that regaining normal functioning of the digestive system was experienced as more painful than what they had expected from the information provided by staff (Wagner, Carlslund, Sørensen & Ottesen, 2005). The women also experienced noticeable and prolonged fatigue after hospital discharge (Wagner et al, 2005). A qualitative case report of one woman's experience with hysterectomy (on a benign indication) reported less postoperative pain than expected. Six weeks postoperatively, there was a feeling of being recovered although there was still "recovery work to be done" (Fleming, 2003). Studies reporting what women with endometrial cancer experience when undergoing surgical treatment are also scarce. Hughes and colleagues conducted a phenomenological study of patient experiences of laparoscopic hysterectomy for endometrial cancer (Hughes, Knibb, & Allan, 2010). This study found that fear of cancer and lacking expert knowledge of the disease led women with endometrial cancer to entrust the surgeon with the responsibility for decision-making. Also the women felt insufficiently informed when having laparoscopic surgery (Hughes et al., 2010).

Health care professionals need to know how women react physically as well as mentally to robotic surgery and how they experience the treatment. During the treatment course, healthcare professionals only have brief contact with women during hospitalisation and in the outpatient clinic. This calls for targeted information and support. Knowledge of the experiences of women allow pre- and postoperative information and care to be individually tailored to a higher degree.

Health-related quality of life

Health-related quality of life (HRQoL) is a patient-reported outcome measure (PROM) and constitutes an important reflection of treatment or disease-related adverse effects (McAlpine et al., 2014). A PROM may be generic or disease-specific. PROMS capture patients' perceptions of symptoms, functioning and well-being (Efficace et al., 2014). Health care professionals need to have detailed knowledge of how women experience the postoperative course in order to provide guidance and reassurance to future women undergoing RALH for endometrial cancer. Studies portraying patient-reported quality of life in women undergoing RALH for endometrial cancer are scarce. Previously HRQoL has been based on physicians' observations

(Ramirez et al., 2012). Similarly, HRQoL in women with endometrial cancer treated by other surgical modes has attracted little attention in research. Nevertheless both short and long term complications of treatment are likely to impact negatively on HRQoL (Joly et al., 2014). The Society of Gynaecologic Oncology in USA recently recommended that patient-reported HRQoL is assessed alongside clinical outcomes in future studies (Gala et al., 2014; Ramirez et al., 2012).

OBJECTIVES

The overall objective of this explorative, descriptive thesis was to evaluate RALH as surgical treatment for women suffering from endometrial cancer. This was done through the following studies, each of which used different research methods.
Each study was planned, conducted and analysed individually without applying any overall theoretical framework in any of the studies or in the thesis as a whole. The studies are not interrelated. Rather, they individually contribute different perspectives on RALH for women with endometrial cancer.

Studies and objectives:

1. A retrospective cohort study exploring the type, incidence and severity of postoperative complications in women treated with RALH for endometrial cancer or ACH (Paper I).

2. A qualitative study exploring how women with endometrial cancer experienced RALH (Paper II).

3. A health economic study comparing costs for RALH and TAH for women with endometrial cancer or ACH (Paper III).

4. A prospective cohort study of HRQoL up to 4 months after RALH (Paper IV).

PRESENTATION OF STUDIES

The four studies in this synopsis are listed in an overview with a description of design, participants, data source, outcome, methods and analysis (Table 1). The following is a brief presentation of the studies, specifically emphasising methodological strengths and limitations. Issues of internal and external validity will be addressed in the quantitative studies (Paper I, III, IV). Internal validity refers to the ability of a study to measures what was originally intended. It is the extent to which the observed difference in outcomes between groups can be attributed to the intervention rather than to other factors (Lu, 2009). Confounding is a factor that predicts outcome and is associated with the exposure. The lower the risk of confounding in a study, the higher the internal validity. Selection bias, information bias, and confounding are present to some degree in all observational research (Grimes & Schulz, 2002b) and will be addressed in detail in relation to each paper. External validity refers to the generalisability of results to other populations or situations.

In relation to the qualitative study (Paper II) preconceptions will be discussed, and trustworthiness will be explored focusing on credibility (in preference to internal validity), dependability (in preference to reliability) and confirmability (in preference to "objectivity") and lastly, transferability (in preference to external validity). The full descriptions of the studies are in appendix 2-5

Tabel 1:

Study	**Paper I**	**Paper II**	**Paper III**	**Paper IV**
Design	Retrospective decriptive cohort study	Qualitative study	Activity based costing study	Prospective cohort study
Participants	n= 235 women treated by RALH with EC or ACH	n= 12 women treated by RALH (from paper IV)	n= 360 women treated by TAH or RALH	n= 139 women treated by RALH
Data source	Medical records	Women treated in Department of Gyn. HEH.	Medical records and Danish Anaesthesia Database	Women treated in Department of Gyn. HEH.
Outcome	Severity of postoperative complications	Experience with RALH	Costs differences	HRQoL, symptoms and function and time to reassume habitual activity
Methods	Follow-up for 12 months	Semi structured interviews	Activity-based costing – analysis	Survey at baseline, 1 and 5 weeks and 4 months after surgery
Analysis	Two - sample t - test, Fisher´s exact test	Qualitative content analysis	Independent t-test (bootstrap). Ordinary least squares regression.	Mixed effects model and Non-Parametric Wilcoxon Signed Rank test

Paper I: Robotic-assisted laparoscopic hysterectomy seems safe in women with early-stage endometrial cancer

The aim was to explore the types and incidence of complications according to the Clavien-Dindo scale after RALH for early stage endometrial cancer and atypical complex hyperplasia (see appendix 2).

Method: We conducted a retrospective descriptive cohort study with 12 months follow-up. The primary outcome was incidence of complications grade ≥ 3 according to the Clavien-Dindo scale (see appendix 1) and the secondary outcome was overall complications requiring treatment. Data were collected from patient records.

Results: We included 235 women with endometrial cancer or ACH. A total of 6 % developed grade 3 or higher complications with no difference between women who had PLA or not (p= 0.24). The overall incidence of complications was 15 %, likewise with no difference between groups (p= 0.32). The most frequent complications were urinary tract infections (6 %) and port site/wound infections (3 %). Twenty-one per cent of the women who had lymphadenectomy developed lymphedema within 12 months.

Strengths & Limitations

A limitation of this study is the use of retrospective data. Internal validity can be compromised by using retrospective data as only pre-existing data are available. Data were originally documented for another purpose - patient treatment and care (Berbano & Baxi, 2012; Euser, Zoccali, Jager, & Dekker, 2009). Our data on the development of lymphedema serve as an example. The incidence of lymphedema might have been different (presumably higher) if we could have obtained prospective data on the condition of lower extremities in all included women. In this study we had to rely on available data and, subsequently, we defined lymphedema as present if the women were referred by the gynaecologist (in the outpatient clinic for the regular follow-up visits) to the physiotherapist and if they were diagnosed with lymphedema and staged within 12 months after surgery. Another limitation of retrospective data is the higher risk of missing data. A few missing observations are of minor significance, but a large amount of missing data can be a major

threat to the integrity of a study (Altman & Bland, 2007). The question is if the available data are biased. Missing data are a threat to the internal validity.

In this study, a limitation was the lack of a comparison with alternative surgical methods. Studies with no control group do not allow conclusions about associations, causal or otherwise (Grimes & Schulz, 2002b). Descriptive studies are often a precursor for more rigorous studies with comparison groups, as in this thesis. Common pitfalls of descriptive reports include an absence of clear, specific, and reproducible case definitions, and interpretations that go beyond data (Grimes & Schulz, 2002b). We had a clear case definition but one could argue that stating that the surgery is safe and well tolerated is a disputable claim when it is not compared to an alternative.

A strength of this study was the validating process of data collection and the use of a protocol for data retrieval. By using a protocol and being two assessors who gathered data independently and by using an arbitrator to settle differences we sought to reduce information bias.

Another strength was the use of the validated Clavien-Dindo scale specifically suitable for retrospective analysis of postoperative complications (Dindo, Demartines, & Clavien, 2004). The strength of this tool is that it does not categorise into major and minor complications. Rather it grades complications according to treatment needed (Wechter et al., 2014). It has previously been addressed that different definitions of complications makes comparison difficult (Franchi et al., 2001).

In the present study we considered it a strength that we observed women for 12 months. Surgically related complications such as hernia, vaginal dehiscence and vaginal prolapse typically develop later than 30 days postoperatively.

Selection bias was not an issue in this study as all patients were included consecutively within the timeframe March 2009 until December 2012. However, it is possible that the results may be negatively influenced by the fact that we included learning cases as the debut for RALH at our institution was in fact in March 2009.

As for external validity this study had broad inclusion criteria and few exclusion criteria, strengthening the external validity. Our results are comparable to other cohorts in the literature (Fagotti et al., 2012; Wechter et al., 2014), however in our sample we only have women who had simple hysterectomy and only *pelvic* lymphadenectomy was performed. In several studies of women with endometrial cancer in the literature the case mix comprises radical hysterectomy (Raffaello et al., 2015) and some report outcomes after both *pelvic* and *para-aortic*

lymphadenectomy (Boggess et al., 2008; ElSahwi et al., 2012). The latter are surgical procedures that might increase postoperative complications even more.

Conclusion

We found a 6 % rate of severe complications in women with endometrial cancer or ACH within 12 months. Urinary tract infections and port site infections were the most frequent types of complications. The rate of complications was comparable to other studies with RALH for malignant conditions. It is possible that the sample size in the subgroup of women with PLA was too small to reproduce the findings of an increased rate of complications seen in previous studies.

Paper II: The experience of Robotic-assisted laparoscopic hysterectomy for women treated for early-stage endometrial cancer – A qualitative study

The aim was to investigate how women diagnosed with early-stage endometrial cancer experienced robotic-assisted laparoscopic hysterectomy (see appendix 3).

Method: This was a qualitative study. Data were obtained by semi-structured interviews, transcribed verbatim and organised with NVivo software. We analysed through data-driven coding with content analysis as described by Graneheim and Lundman in 5 steps (Graneheim & Lundman, 2004). Audit trails were made after every interview and transcription. All co-authors were involved in the analysis and confirmed categories and themes.

Results: We interviewed 12 women on average 12 weeks after surgery (range 6-19). The 4 overarching themes were: “Surgery was a piece of cake”, “Recovering physically after surgery”, “Going from being off guard to being on guard” and “Preparing oneself by seeking information”. We found that the women had trust in the robotic technique, and they experienced fast physical recovery after RALH. Despite the MIS they experienced fatigue and painful bowel movement after discharge. Uncertainties and unanswered questions remained in the postoperative period after the first follow-up visit. Women searched for information from various sources: the internet and the online patient chart in order to prepare for surgery and to come to terms with the diagnosis. Shortly after discharge, the women did not consider themselves surviving cancer patients, but felt cured although they had an underlying fear of cancer recurrence.

Strengths & Limitations

Confirmability addresses the question of whether study findings reflect the experiences and concepts of informants rather than the qualities and preferences of the researcher (Tobin & Begley, 2004). In this study reporting of findings was supported by quotations. To further ensure confirmability we could have documented our own preconceptions prior to data collection. We did not do so and this is a potential limitation. Although not documented the preconceptions were: women would experience pain postoperatively and be apprehensive towards undergoing RALH.

A strength of the study was the stringent analytical process and the fact that the four authors had different clinical perspectives and distance to the data and informants. In this way more perspectives were included in the design and analysis thus challenging individual preconceptions. This supports the credibility and dependability of the study.

An inherent risk was social desirability bias. Social desirability bias is when the informant expresses views thought to please the interviewer. It was a concern already in the planning of the study. When conducting a study evaluating a treatment, one has to bear in mind that the researcher is also a health care professional and the informant a recipient of care.

It was a strength that we used content analysis as it is a relevant method for analysis due to the flexible and pragmatic approach with the possibility of covering both a manifest and latent content (Hsieh & Shannon, 2005). The latter involves deeper meaning and therefore requires further interpretation. Content analysis has the advantage of not imposing preconceived categories or theoretical perspectives on data (Hsieh & Shannon, 2005). Some argue that content analysis can fail to develop a complete understanding of the explored context (Hsieh & Shannon, 2005), however our findings were largely in line with those of a previous phenomenological study of laparoscopy (Hughes et al., 2010).

Although not specifically recommended in content analysis, we systematically used audit trail memos (Crabtree & Miller, 1999) after interviews and after transcription of interviews. Memoing originates from the Grounded Theory approach (Cresswell J. W., 2012) and is a useful tool to contain preconscious processing, analysis and reflections from the researcher, thereby enhancing dependability. In this study, memoing was used both for reflection on the quality of the interview (setting, contact, questions) as well as the data (answers, expressions and silences).

We used a criterion sample (Crabtree & Miller, 1999) because we wanted varied representation of women living alone and women still in the workforce. The reason for this was that we believed these experiences were important for transferability and credibility. We approached women who were already included in study IV and specifically targeted women who were able to express their experiences in a detailed manner and who were able to reflect on the treatment trajectory. Recruitment was facilitated by prior contact and we considered this a strength. However, methodological concerns were that women in the interview study were selected from an already selected group, presumably those resourceful enough to participate in two research studies. This potential selection bias could be considered a limitation. It is likely that women who were very positive towards the robotic approach were also more prone to accept the invitation to participate in

the qualitative study. Reasons for not wishing to participate were the need to dissociate from the experience altogether and not having time.

In qualitative research the objective is not to generalise results beyond the case, but to understand the complexity of the case (Cresswell J. W., 2012; Malterud, 2001), leaving it up to the reader to conclude if the results are transferable to other contexts and settings (Shenton, 2004).

In the present study it was a strength that we reported according to the Consolidated Criteria for Reporting Qualitative Research (COREQ) – a 32-item check list (Tong, Sainsbury, & Craig, 2007) of relevant items.

Conclusion

The women were primarily concerned with their cancer illness rather than the surgical treatment; they were positive towards the robotic approach and felt recovered shortly after surgery. Knowledge gaps were revealed concerning insufficient understanding of the new anatomy, the normal course of vaginal bleeding and the duration of painful bowel movement postoperatively.

Paper III: Cost analysis of robotic-assisted laparoscopic hysterectomy versus total abdominal hysterectomy for women with endometrial cancer and atypical complex hyperplasia.

The aim was to provide an economical evaluation by presenting a comprehensive Activity-Based Costing calculation of RALH for women suffering from endometrial cancer or ACH and to identify critical costs components in comparison with TAH (see appendix 4).

Method: We conducted an economic evaluation using an activity-based costing (ABC) model. In the model we included consumables, salaries of health care professionals. Cost drivers were severe complications, duration of surgery, anaesthesia and stay in the PACU as well as LOS. The main outcome was the cost difference in Danish kroner (DKK) between RALH and TAH. Differences between groups were calculated by independent samples t-tests with bootstrapping (n=1000) and sensitivity analyses were performed to explore the model further. Exploration in costs was done by Ordinary least squares regression.

Results: The analysis was based on 202 women treated by RALH (in 2013-2014) and 158 women treated by TAH (in 2006-2009). The average cost for consumables for TAH was 12.642 DKK cheaper than for RALH (2014 price level: 1€ =7.5 DKK.). When including all cost drivers, the analysis showed that the RALH procedure was 9.386 DKK cheaper than the TAH (17 % cheaper than THA) (p=0.003). When the robot investment was included as costs, the cost difference was reduced to 4.053 DKK (RALH was 7 % less costly than TAH) (p=0.2). Regression analysis showed that increasing age and Type 2 diabetes seemed to increase the overall costs.

Strengths & Limitations

A limitation in the present study is the lack of societal data to give a more complete description of what is gained or lost by RALH in terms of time to recover to normal activity, time to return to work for those employed and the number of visits to the general practitioner (GP). Unfortunately this was not possible to analyse as we did not have any access to data after discharge.

A strength is the use of the ABC modelling because of the application of detailed data on important cost drivers. These data give more accurate costs and insights into the cost structure (Dombrée et al., 2014). Changes in cost drivers will cause changes in the total treatment cost and

thereby give insight into potential consequences of different treatment patterns, thus making the ABC - method a valuable managing tool (Ramsey RH, 1994).

In our model, cost drivers were meaningful, resource homogenous and relevant to the overall costs. It strengthens the internal validity that cost drivers were calculated from actual patients, who were treated by the two surgical methods rather than based on theoretical assumptions or expert guesses. Patient driven data originated from patient journals and registers. However, data was gathered retrospectively and there was a significant time gap between the two cohorts. This is a limitation of the study.

LOS has a substantial impact on the overall cost of hospitalisation (Iavazzo et al., 2014). As found in other studies (Lau et al., 2012; Bell MC, Torgerson J; Seshadri-Kreaden U, Suttle AW, 2008; Teljeur et al., 2014) LOS was the driving factor in the higher cost for the comparison group to RALH. However, reducing LOS has been a policy aim for many health care systems during the last decades and is thought to indicate efficiency. There are managerial and financial incentives to reduce LOS (Clarke & Rosen, 2001). We assume that some of the difference between LOS in the two cohorts was confounded by time alone.

As cost data are seldom normally distributed, we conducted an independent samples t-test with Bootstrapping (n=1000), a method of resampling that controls and tests the robustness of results. It is a non-parametric statistical method simulating more samples. Increasing the number of samples cannot increase the amount of information in the original data but can improve the accuracy of the standard errors and confidence intervals.

Finally it was a strength that we have documented the study using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) (Husereau et al., 2013). When conducting economic evaluations it is imperative that all choices, reasoning and estimations of quantities and prices are documented with a fair amount of accuracy (Drummond, Sculpher, O'Brien, 2005) enabling the calculations to be reproduced if necessary.

Conclusion: For women with endometrial cancer or ACH, RALH was less costly compared to TAH by providing better outcomes for women with shorter LOS and less severe complications counterbalancing the high cost for the actual robotic surgery.

Paper IV: Health-related quality of life after robotic-assisted laparoscopic hysterectomy for women with endometrial cancer - A prospective cohort study

The aim was to explore changes in HRQoL, functioning and symptoms during the first four months after RALH for women with endometrial cancer or ACH (see appendix 5).

Method: We conducted a prospective cohort study using a generic (EQ-3L-5D) (see appendix 6) and an illness specific (EORTC C-30 and EN-24) (see appendix 7) questionnaire of HRQoL, function and symptoms. The women answered questionnaires at baseline before surgery, 1 week, 5 weeks and 4 months after surgery. Data were obtained face to face at baseline and, after discharge, by telephone. The repeated measures were analysed predominantly by the linear Mixed model. Furthermore women were asked to self-rate their health status at baseline and after the 4 months by a single item question. The women were asked to report their level of activity weekly during the first 5 postoperative weeks in a patient diary.

Results: We included 139 women, of these 135 completed the final measurements after 4 months. General health score was above baseline after 5 weeks suggesting that RALH does not negatively affect general health in women with endometrial cancer 5 weeks after surgery. Fatigue, pain, constipation, gastrointestinal symptoms and appetite were negatively affected at 1 week and resolved shortly after. Role functioning (performing work or hobbies) and change of taste was not completely back to baseline level by 5 weeks but improving.

Strengths & Limitations

It was a pragmatic choice to include women and conduct baseline data collection on the last weekday before surgery; unfortunately several women were very anxious at this point. We suspect that timing had a negative influence on the women's inclination to participate (n=29 declined participation) and score. Our drop-out analysis showed that women included in the study had less comorbidity than those who chose not to participate, thus producing a selection bias by healthy entrant effect (Sedgwick, 2014). This may affect the external validity of the study.

It strengthens the internal validity that we used a prospective design with validated questionnaires to capture general and illness specific HRQoL issues.

After pilot testing, we decided only to use the above mentioned questionnaires as we wanted to reduce survey or response fatigue (Choi & Pak, 2005; Porter, 2004) to strengthen internal

validity. Data collection took from 15 to 45 min. depending on the participants' need for explanations and additional questions. Nevertheless, it was a strength that we telephoned women for follow-up and had a fair rate of women who answered at all 4 time points. Missing forms were at random. In total, only 3 % were lost to follow-up. We believe that the telephone approach and consistency in data collection increased the women's obligation to continue participation.

We found that many women had experienced changes in symptoms and functions between 1 and 5 weeks. In hindsight it might have been preferable to measure responses at week 2, 3, and 4 as this might have enabled us to conclude more specifically when changes occurred. A strength was the multiple time points of measurement to uncover the development during recovery but this also introduced a risk of multiple testing and hereby a Type 1 error (Bender & Lange, 2001).

After double data entry we detected a 2 % discrepancy in the two data sheets. This was corrected before analysis and double data entry proved to be a good strategy to ensure valid data.

To characterise change over time we used repeated measurements which generates more statistical power as each individual acts as her own control. The strengths of Mixed model analysis is the ability to accommodate missing values (unbalanced data) (Krueger & Tian, 2004).

Response shift, changing internal values and conceptions of quality of life, is an issue we need to take into consideration when analysing data from HRQoL questionnaires (Sprangers & Schwartz, 1999). Some of the improvement in scoring could be due to adaptation to certain symptoms (psychological adaption) over time.

Conclusion

By using PROMs in clinical practice, health care professionals gain knowledge of the effects of disease and treatment from the patient' perspective. HRQoL was restored 5 weeks after RALH for the majority. Fatigue, constipation, gastrointestinal symptoms, pain, appetite, change of taste were negatively affected short-term after surgery. These HRQoL issues are crucial to include in pre-surgery information and to include in follow-up care programmes.

DISCUSSION

The overall purpose of this thesis was to explore and to portray patient and health outcomes of RALH for women with endometrial cancer and premalignant conditions. Through the four studies, knowledge of postoperative complications, costs, women's experiences and HRQoL has been gained. The results of the four studies also inspired a general discussion of the validity of RCTs versus observational studies in evaluating RALH, differences in post-operative complications according to type of surgery, the importance of health economic evaluations, patients' perspectives through qualitative research and the relevance of PROMs in evaluating treatment outcomes.

Validity of RCTs versus observational studies in evaluating RALH

The discussion about the validity of observational studies versus randomised trials for estimating effectiveness of interventions has been on-going. The RCT has long been the gold standard for clinical research, representing the best way to determine efficacy and effectiveness for interventions (West et al., 2008). In observational studies, participants in pre-existing or constructed groups receive various treatment conditions. The selection of participants into each treatment condition may be associated with confounding factors, resulting in bias (West et al., 2008). The problem with observational studies is that they cannot account for confounders that are unknown and cannot document causalities.

Many publications covering observational studies of robotic surgery call for RCTs to determine if RALH is superior to conventional surgery. However, testing the efficacy of new surgical procedures is very different from testing new drugs where RCTs are warranted. New surgical procedures develop continuously, complications may decrease with use, and results can vary with surgeon experiences. Opposed to this, when testing new drugs, complications may increase with use and the results are unrelated to physician skills (Boncheck, 1997).

There are several plausible reasons why RCTs have not examined the superiority of RALH for women with endometrial cancer in the past. One reason could be lack of clinical equipoise - a lack of uncertainty that one intervention is superior to another (Freedmann, 1987). If genuine uncertainty does not exist patients or health care providers can have preferences and therefore be reluctant to randomise to RALH. Another reason could be that it is considered unethical or unpractical to perform an RCT (Lu, 2009) as the capacity in operating theatres and presence of specialised staff can be a logistic challenge. Furthermore, potential differences in outcomes between laparoscopy and RALH may be so small that large numbers of patients would be

required to detect a statistically significant difference (Ramirez et al., 2012) and funding for such RCTs could be an additional barrier (Bonell et al., 2011). The use of non-randomised studies can be relevant as confirmatory studies of outcomes of an intervention being translated into new settings if previous RCT s have reported benefits and little risk for harm (Bonell et al., 2011) – for instance laparoscopy hysterectomy translated to RALH.

Some researchers in this field speculate that in the future it is unlikely that RCTs will be conducted because of the existing favourable data in laparoscopic treatment of endometrial cancer and the widespread acceptance and implementation of robotic surgery (Backes & Fowler, 2014). When randomised or other controlled studies are not ethically possible, uncontrolled studies may have to be considered the best possible evidence (Thomson et al., 2004).

An overall concern in the robotic literature is that reporting of outcomes frequently comes from proponents of the surgical method (Liu et al., 2014). It is not uncommon that authors have worked as consultants for or are shareholders in the robotic industry (Brudie et al., 2013; Knight & Escobar, 2014; Leitao et al., 2013; Paley et al., 2011; Seamon et al., 2009; Smorgick et al., 2014; Soto et al., 2011) hereby providing a risk of introducing a conflict of interest and bias.

Differences in post-operative complications according to type of surgery

We found that overall 6 % of women with endometrial cancer developed a ≥ 3 Clavien-Dindo complication within 12 months after RALH (Paper I). Several studies have recently assessed postoperative complications using the Clavien-Dindo scale and report complication rates between 2-8 % in women undergoing robotic gynaecologic surgery depending on the precise case-mix and timeframe (Seror et al., 2014; Wechter et al., 2014; Yim et al., 2015). Every complication acquired is a complication too much. However, not all are avoidable. Considering the age and comorbidity characterising women with endometrial cancer combined with the physiologically challenging positioning during RALH, and the duration of surgery, the 6 % rate of severe complications found in paper I can be considered quite low.

Wechter and colleagues argued that complications ≥ 3 in the Clavien-Dindo scale were the most clinically relevant as these complications demand surgical, endoscopic or radiological intervention (Wechter et al., 2014). A well founded critique of the Clavien-Dindo scale is that it does not encompass perioperative complications (Wechter et al., 2014) or define a timeframe for complications to develop. Similar to Lönnerfors and colleagues (Lönnerfors et al

2015), we found a 12 month follow-up period relevant as some surgical complications related to robotic surgery may take several months to develop.

We found no differences in postoperative complications for women also having PLA (Paper I). This is contradictory to other studies in the field (Panici et al., 2008; Kitchener et al., 2009; May & Bryant, 2010) however we suspect it may be due to lack of power in our study.

There are fundamental limitations of our studies (Paper I and IV) as they build on data from a single centre, they have not compared RALH to laparoscopy surgery and they lack cancer specific outcomes as recurrence, survival and stages of disease.

The importance of health economic evaluations

When an intervention is costly there is a strong argument that only an RCT will provide adequate evidence, and therefore barriers to conducting RCTs must be overcome. However, when there is evidence that an intervention is cheap, relatively easy to deliver and there is minimal potential for harm, there is a stronger will to accept evidence from other designs (Bonell et al., 2011).

Health economic evaluations serve to inform resource allocation decisions (Husereau et al., 2013). It can be questioned if an evaluation of a previous treatment option (TAH) in comparison to a newly implemented standard treatment (RALH) is relevant. However, in the health care system there is an on-going intense debate of prioritising and whether the robotic approach is cost-effective. The debate is fired by the increasing economic pressure on the health care system. For this reason we found the research question justified at the present point in time.

When conducting a health economic evaluation, it is evident that the economic analysis cannot have more quality than the clinical study or data upon which it builds (Drummond et al, 2005). Consequently, retrospective data from two cohorts with a substantial time gap is a limitation in a health economic evaluation. Economic evaluation is moreover a product of the researcher's choices of which variables to include in the analysis, and in the model building process the decisions are numerous. The model building depends on what is included and what is left out in calculations, what type of data are available and can be priced and which results are usable in practice. Therefore it is imperative that the reporting is transparent in order to understand how the conclusions are reached.

The diagnosis-related group (DRG) system is used for hospital reimbursement and for benchmarking performance (Serdén & O'Reilly, 2014). Originally we had hoped to be able to use

patient specific coding by DRG in our model for analysis in study 3. After exploring actual DRG data from the two time periods we concluded that the time gap was too large. The DRG codes are altered a little every year and as coding practices differ over time we did not find data reliable enough for analysis or comparison over time. In the early start of robotic surgery at our institution we did not even have codes for robotic surgery. We decided instead that we would use clinical data from patient charts and price severe complications according to the DRG Fee-system (Statens Serum Institute, 2014) which we considered more valid approach.

In our activity-based costing model we included cost drivers such as operative time, LOS and complications and found that less severe complications and shorter LOS made RALH a cost effective alternative to TAH counterbalancing the high cost for the consumables during robotic surgery (Paper III). Eklind and colleagues found equal cost between laparotomy and RALH (Eklind, Lindfors, Sjöli, & Dahm-Kähler, 2015). Previous studies comparing RALH with laparoscopy and laparotomy for endometrial cancer found robotic surgery to be more cost effective than laparotomy but laparoscopy was presumed the most cost effective of the three surgical modes (Barnett, Judd, & Wu, 2010; Shah et al., 2011). Several studies including women with endometrial cancer comparing robotic and laparoscopic surgery found that RALH remained more costly than laparoscopic hysterectomy (Desille-Gbaguidi et al., 2013; Holtz, Miroshnichenko, Finnegan, Chernick, & Dunton, 2010; Turunen, Pakarinen, Sjöberg, & Loukovaara, 2013; Wright et al., 2014). Overall RALH seems to be more cost effective than TAH for women with endometrial cancer when including LOS and complications. However, conventional laparoscopic surgery might be even more cost effective

Patient's perspectives through qualitative research

Qualitative studies help to provide rich descriptions of phenomena and enhance understanding of the context of events as well as the events themselves. When the aim is to evaluate an intervention (in this thesis: RALH) the "rich description" derived from qualitative methods can result in a more complete description of the intervention (Sofaer, 1999). Rigor in reporting can oblige the critique that qualitative research can be non-transparent and unstructured thus making it less trustworthy (Shenton, 2004).

The women in the study 2 were understandably primarily focused on their cancer illness and secondly on the surgical mode as seen in a previous qualitative study exploring laparoscopy (Hughes et al., 2010). If we had chosen women with benign diagnoses to explore

experiences with RALH, it is possible that we might have had greater focus on the surgical treatment and less on the gynaecological illness. Furthermore, interviewing before the actual surgery could potentially have revealed more uncertainties and reservations.

To our knowledge there are no previous studies covering the qualitative experience of RALH. We found that women considered RALH "easy to overcome" but also "mysterious" as they did not comprehend how it was performed. They felt recovered shortly after surgery; with the exception of prolonged bowel discomfort and tiredness (Paper II). Pain in connection with the first bowel movement after surgery has previously been reported in minimally invasive urogynecology (McNanley et al., 2012). Tiredness has also been documented earlier as reported by DeCherney and colleagues who found that fatigue was a highly prevalent post-hysterectomy symptom with substantial negative physical, psychosocial, and economic effects on patients during recovery (DeCherney & Bachmann, 2002). The women had unanswered questions about the actual treatment trajectory during their hospital stay and, after hospital discharge; they had several misconceptions about their novel anatomy (Paper II). Similar to our findings, Bowes and colleagues found that some women were unsure why cervical smear tests did not detect endometrial cancer and whether the cervix was removed during hysterectomy (Bowes et al., 2014). We found that some women did not associate vaginal bleeding with the surgery itself. Rather, they speculated whether it was a sign of infection or of remaining cancer, or in fact, if the cancer had spread. In this way postoperative bleeding rekindled fear (Paper II). Hughes and colleague's found that women treated with conventional laparoscopy also perceived vaginal bleeding as loss of control and as an awareness of the body (Hughes et al., 2010). For health care professionals to be able to provide women with information and support pre- and postoperatively, it is imperative to have knowledge of lay understanding and potential misconceptions as well as postoperative symptoms.

In the qualitative paradigm the research must aim at representing the voices of the affected persons. Qualitative research develops as a result of the interaction between the interviewer and the informant. The researcher can never be invisible; however the aim for the researcher is to keep in the background (Malterud K., 2003). For reflexivity, researchers must position themselves by conveying their background and preconceptions and how this might affect the validity of the study (Cresswell J. W., 2012). My background (being woman, 5-10 years younger than informants, and a nurse without prior clinical experience in gynaecology or robotic-assisted surgery) and preconceptions (women would experience pain postoperatively and be apprehensive towards undergoing RALH) could potentially have influenced the results of this study. However, we believe

that the fact that the analysis was done by several researchers together, all with different perspectives and distance to the field, increased reflexivity and there by the validity of the study.

Outcomes of qualitative research are, at best, only a version of the truth (Hewitt, 2007). However qualitative research should always have the ambition to produce results that have impact and lead to a benefit for patients (Hewitt, 2007). The findings from study 2 have been incorporated in the newly opened Nursing Outpatient Clinic that counsels women postoperatively at the Department of Gynaecology and can hopefully benefit women there.

A combination of qualitative and quantitative studies can improve an evaluation of an intervention by ensuring that the limitations of one type of study are balanced by the strengths of another. Qualitative and quantitative research can be combined in mixed methods studies where quantitative and qualitative studies are conducted sequentially or concurrently (Creswell & Zhang, 2009). This thesis was not designed as a mixed methods study. However the qualitative study (Paper II) provides nuances to some of the quantitative findings (Paper IV), by uncovering details and lay understanding that cannot be captured by any other method.

The relevance of patient-reported outcome measures

In recognition of the lack of evidence for the effect of control visits after cancer treatment on survival (Agboola, Grunfeld, Coyle, & Perry, 1997), changes are being made in the follow up programme in Denmark. All affected women have previously been offered routine outpatient control visits for 3 years after surgery for endometrial cancer (Danish Health and Medicines Authority , 2012). From June 2015, this changed towards more individually tailored follow-up visits focusing on empowering the women to observe and react to symptoms of possible recurrence (Danish Health and Medicines Authority, 2015b). In light of this change, it is even more relevant to expand health care professionals' knowledge of women's experiences of HRQoL, symptoms and function in the short and long term after RALH.

We found HRQoL was restored to the preoperative level within 5 weeks after RALH (Paper V). During the first postoperative weeks, the ability to perform work and hobbies, pain, fatigue, constipation, gastrointestinal function, appetite, change of taste were all negatively affected (Paper IV). Other studies have likewise endeavoured to describe HRQoL in the recovery period after RALH. Vaknin and colleagues asked women with endometrial cancer to rate their postoperative health on a five point scale (1 being much better and 5 being much worse) 4 weeks after RALH and found a mean value of 2.3 (Vaknin et al., 2010). Lau and colleagues used a self-

constructed questionnaire and found that 40 % rated increased QoL and 52 % felt it was unchanged after RALH (Lau et al., 2014). Jeppesen and colleagues conducted a mixed methods study of short term needs (3 months after laparoscopic hysterectomy or open hysterectomy for cervical or endometrial cancer) (Jeppesen, Mogensen, Dehn, & Jensen, 2015). They found that women with endometrial cancer experienced a significant increase in constipation, lymphedema, and fatigue (Jeppesen et al., 2015).

Although it was not the aim of study 4, several women expressed that they were motivated to participate in the study as they felt a sense of security by being contacted by health care professionals during the first weeks and months of recovery. Danish patients' willingness to participate in studies has previously been explored and the motives identified were altruism and an expectation of receiving more individual attention. The latter was linked to the feeling of being "handpicked" and receiving more close monitoring than if outside the trial setting (Madsen, Holm, & Riis, 1999; M. Madsen et al., 2002).

To describe HRQoL, functioning and symptoms in study 4 we used repeated measures. Repeated measures produce more accurate estimates and more certain conclusions about changes over time because pairs of repeated measures from the same individual are likely more similar than single observations obtained from two randomly selected individuals, thereby eliminating variability among individuals (Fitzmaurice et al, 2011).

Clinical significance must always be considered alongside statistical significance. A study can show statistically significant differences in two treatment options but may lack clinical relevance for patients (Bhardwaj, Camacho, Derrow, Fleischer, & Feldman, 2004). In study 4, we considered both statistical and clinical significance. The Mixed Model Analysis showed which variables had a statistically significant change over the four time points. However, clinically significant changes were determined as changes exceeding 10 % from one time point to another as previously suggested (Osoba et al, 1998; Maringwa et al., 2011; Ringash, O'Sullivan, Bezjak, & Redelmeier, 2007).

Knowing when the women resumed their habitual level of activity was considered very important when we planned study 4. However, it proved difficult to measure. We tried to encompass the baseline variability in activity because the variation in the women's habitual level of activity was significant. Some women were extremely active in the working force and doing strenuous sports, while others were immobilised in their home with a home help or a spouse to aid them. Earlier studies have tried to capture this dimension of activity by measuring days to return to

normal activity (Eklind et al., 2015; Bell MC et al, , 2008), or similar to our study: self-reporting of percentage of return to normal baseline activity (Kornblith et al., 2009; Paraiso et al., 2013). We found a higher percentage of return to habitual daily level of activity at 5 weeks than previously seen for laparoscopy and even more so compared to for laparotomy after 6 weeks (Kornblith et al., 2009).

CONCLUSION

RALH as treatment for women with endometrial cancer appears well tolerated and our results, bearing in mind their strengths and limitations, also suggest that it is safe. Women developed few severe complications after RALH and we could not detect that PLA increased the frequency of complications. We found it useful to include 12 months follow up as it captured surgical complications that took longer time to develop. The Clavien-Dindo scale proved a relevant tool for evaluating severity of complications in a way that enables comparison across populations. Our results suggest that women treated by RALH for endometrial cancer developed fewer and less severe complications compared to the previous standard treatment – TAH. RALH resulted in a reduced LOS compared to TAH. Less severe complications and shorter LOS made RALH a more cost effective alternative to TAH. RALH was most cost effective even when complications were excluded from the analysis. Increasing age and Type 2 diabetes seemed associated with increasing costs.

The women who were interviewed after surgery considered RALH "easy to overcome" and felt recovered shortly after surgery; all in all they expressed a positive attitude towards the new technology. They had unanswered questions about the actual treatment trajectory during their hospital stay and after hospital discharge, they were unsure of the natural course of bleeding and bowel function. The women reported their HRQoL was restored to the preoperative level within 5 weeks after RALH. During the first weeks, their ability to perform work and hobbies, pain, fatigue, constipation, gastrointestinal function, appetite, change of taste were negatively affected.

As indicated in the discussion of methodology, RCTs of robotic-assisted surgery versus conservative surgical approaches are presumably no longer feasible. Observational studies with high external validity examining RALH for women with endometrial cancer in real life scenarios will presumably continue to be published and may have significant value if they are carefully conducted, avoidable biases are eliminated and possible pitfalls of the observational design are carefully addressed.

RALH remains a relatively novel surgical approach that will possibly be used progressively with widening indications. It is therefore recommended that women with early stage endometrial cancer undergoing RALH are carefully monitored for postoperative complications using the Clavien-Dindo Scale up to 12 months postoperatively. Furthermore it is recommended that qualitative studies in this field are conducted in order to broaden our knowledge of patients'

expectations and experiences of this approach to surgery. I also suggest that future studies include PROMS to monitor HRQoL, symptoms and function after RALH. This will help health care professionals optimise and target information and care for patients.

Implications for practice and for future research

The studies in this thesis have some implications for clinical practice and for future research:

- Use of validated illness specific HRQoL questionnaires (PROMs) in the nursing outpatient clinic to continuously obtain patient data for quality development, future research and benchmarking with other treatment options and other centres treating women with endometrial cancer.

- Continuous monitoring of post-operative complications using the Clavien-Dindo Scale up to 12 months after RALH and reporting of data to a national gynaecological database, for example The Danish National Clinical Database for Gynaecological Cancer (DGCG, 2014) is recommended.

- Exploring experiences of robotic surgery for women with benign gynaecological diagnoses through qualitative interviews - before and after surgery.

- Use of validated illness specific questionnaires to assess if sexually related problems resolve after 4 months in women treated by RALH for endometrial cancer.

- Exploring recovery after RALH using the newly developed Postoperative Quality Recovery Scale (Royse et al, 2010). The instrument covers several domains (physiologic, nociceptive, emotive, activities of daily living, cognitive, and overall patient perspective) to explore the concept of return to or improvement compared to the pre-surgical state.

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APPENDICES

1: Clavien-Dindo scale

2: Paper 1

3: Paper 2

4: Paper 3

5: Paper 4

6: EQ-5D-3D

7: EORTC QoL C-30 and EN-24

APPENDIX 1

Clavien-Dindo score

Classification of Surgical Complications	
Grade	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions Allowed therapeutic regiments are: drugs as antiemetics, antipyretics, analgesics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications Blood transfusions and total parenteral nutrition are also included
Grade III	Requiring surgical, endoscopic or radiological intervention
Grade IIIa	Intervention not under general anaesthesia
Grade IIIb	Intervention under general anaesthesia
Grade IV	Life-threatening complications (including CNS complications)* requiring IC/ICU management
Grade IVa	Single organ dysfunction (including dialysis)
Grade IVb	Multiorgan dysfunction
Grade V	Death of a patient
Suffix "d"	If the patient suffers from a complication at the time of discharge, the suffix "d" (for "disability") is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.

*Brain hemorrhage, ischemic stroke, subarachnoid bleeding, but excluding transient ischemic attacks,
CNS, central nervous system; IC, intermediate care; ICU, intensive care unit.

(Dindo, Demartines, & Clavien, 2004)

Robotic-assisted laparoscopic hysterectomy seems safe in women with early-stage endometrial cancer

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ABSTRACT

INTRODUCTION: Robotic surgery is increasingly used in the management of endometrial cancer; and although it is known that minimally invasive surgery reduces post-operative morbidity, the outcomes of this novel treatment should be monitored carefully. The aim of this study was to examine the incidence of complications according to the Clavien-Dindo scale after robotic-assisted laparoscopic hysterectomy (RALH) for early-stage endometrial cancer and atypical complex hyperplasia. The Clavien-Dindo scale grades the severity of complications.

METHODS: This was a retrospective, descriptive cohort study of 235 women with endometrial cancer or atypical complex hyperplasia who had RALH. Surgeries were stratified into two groups: with or without pelvic lymphadenectomy.

RESULTS: A total of 6% developed a grade 3 or higher complication with no significant difference (p = 0.24) between the groups. The overall incidence of complications was 15%, also with no significant difference between groups (p = 0.32). The most frequent complications were urinary tract infections (6%) and port site/wound infections (3%). A total of 21% of the women who had lymphadenectomy developed lymphoedema within 12 months.

CONCLUSION: The types and frequency of complications observed in this study resemble those reported in similar studies of RALH for malignant gynaecologic conditions. Health-care professionals treating and caring for women with early-stage endometrial cancer should know of the types and frequency of post-operative complications following RALH.

FUNDING: not relevant.

TRIAL REGISTRATION: not relevant.

Robotic surgery is increasingly being used in the management of endometrial cancer (EC) [1]. Although it is known that minimally invasive surgery reduces post-operative morbidity and patient discomfort [2], the outcomes of this novel treatment should be carefully monitored. The robotic technique has been used in Denmark in gynaecology since 2008 and at Herlev Hospital since 2009. Compared with traditional laparoscopy, robotic-assisted laparoscopic hysterectomy (RALH) has the advantage of 3D-vision, higher magnification, greater precision, a shorter learning curve and better ergonomy for surgeons. The disadvantages are lack of tactile feedback and high costs [2].

The most common gynaecological cancer in the developed world is EC with an incidence of 11-20 per 100,000 women in Europe [3]. In Denmark, the incidence has been constant over the past 20 years with approximately 750 new cases diagnosed annually [4]. The standard treatment is hysterectomy and bilateral salpingo-oophorectomy (BSO). Lymph node involvement is an important prognostic factor [5], and in Denmark cases with more than 50% myometrial invasion (MI) or high-risk histology are offered pelvic lymphadenectomy (PLA). The risk versus benefit of lymphadenectomy in women with clinical stage I EC is a constant subject of debate [6, 7]. The aim of this study was to examine the types and incidence of complications according to the Clavien-Dindo scale after RALH for early stage EC and atypical complex hyperplasia (ACH).

METHODS

This explorative retrospective descriptive study included women with EC or ACH who underwent RALH at Herlev Hospital between March 2009 and December 2012. In all cases, a four-arm da Vinci S or da Vinci Si robot (da Vinci Surgical System, Intuitive Surgical Inc, CA, USA) was used. All the women had a simple hysterectomy and BSO. PLA was performed when more than 50% MI was present or when indicated by high-risk histology. Infracolic omentectomy was performed in case of serous or clear cell carcinoma. The women received a single dose of prophylactic antibiotics at the beginning of surgery and low-molecular heparin and anti-thrombotic stockings during the hospital stay.

All post-operative complications were classified according to the Clavien-Dindo scale (Appendix) [8]. The primary outcome was the incidence of complications grade ≥ 3 according to the Clavien-Dindo scale as these complications are considered clinically significant and include severe complications [9]. The secondary outcome was the incidence of overall post-operative complications requiring treatment.

We assessed the incidence of overall complications as follows: intraoperative complications (lesions of organs), estimated blood loss > 500 ml, any infections requiring antibiotic treatment within 30 days (port site/

ORIGINAL ARTICLE

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TABLE 1

Preoperative characteristics

	HYS + BSO (N = 167)		HYS + BSO + PLA (N = 68[a])			Total (N = 235)	
	mean (SD)	n (%)	mean (SD)	n (%)	p-value	mean (SD)	n (%)
Age, yrs	67.3 (10.09)		69.7 (8.1)		0.1[d]	68 (10.2)	
Menopausal							
Premenopausal		15 (9)		2 (3)			17 (7)
Postmenopausal		152 (91)		66 (97)			218 (93)
Body mass index, kg/m²	29.5 (7.5)		26.9 (4.9)		0.01[d]	28.7 (7.0)	
Obesity class III > 40 kg/m²		19 (11)		1 (1)			20 (9)
Smoking							
Never smoked		91 (54)		33 (49)			124 (53)
Stopped smoking		44 (26)		19 (28)			63 (27)
Smoker		15 (9)		11 (16)			26 (11)
Alcohol consumption							
≤ 7 units/week		110 (66)		39 (57)			149 (63)
> 7 units/week		38 (23)		22 (32)			60 (26)
ASA score							
I		26 (16)		14 (21)			40 (17)
II		106 (63)		50 (88)			156 (66)
III		24 (14)		2 (3)			26 (11)
Cardiovascular disease[b]		95 (57)		37 (54)			132 (56)
Respiratory disease[c]		20 (12)		3 (4)			23 (10)
Diabetes type 2		26 (16)		10 (15)			36 (15)

ASA = American Society of Anesthesiologists; BSO = bilateral salpingo-oophorectomy; HYS = hysterectomy; PLA = pelvic lymphadenectomy; SD = standard deviation.
a) 16 women in this group also had infracolic omentectomy.
b) Definition: hypertension, atrial fibrillation, arteriosclerotic heart disease, heart failure. New York Heart Association Classification of Heart Failure: 1) cardiac disease, but no symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, climbing stairs etc., 2) mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
c) Definition: chronic obstructive pulmonary disease, asthma, emphysema.
d) Independent sample T test.

wound-, lung-, urinary tract- or vaginal cuff infection), any circulatory events (deep vein thrombosis, pulmonary embolism), respiratory events, abdominal events (ileus), urogenital events (acute tubular necrosis) or neurological events (stroke) requiring treatment within 30 days. Hernia, vaginal cuff dehiscence and vaginal prolapse were monitored within 12 months as these complications are surgically related, but may occur later. Lymphoedema occurring within 12 months was considered separately as a disability according to the Clavien-Dindo scale (Appendix).

We reported length of stay (LOS) by calculating the day of surgery as day one and summing the number of days the women were hospitalised. Two data assessors (SH, MH) independently assessed data from hospital records to minimise bias, and an arbitrator (TT) settled any disagreements. All data were stratified according to whether lymphadenectomy was performed or not. We analysed data using descriptive statistics. Fisher's exact test was used for categorical variables and independent sample T-tests for continuous variables. The Mann-Whitney U test was used when data were not normally distributed. Binary logistic regression was used to examine the influence of the following factors on the risk of post-operative complications: cardiovascular disease and body mass index (BMI). All tests were two-sided, and $p < 0.05$ was considered statistically significant. Data were analysed using SPSS version 19.9 (Inc., Chicago, Illinois, USA).

ABBREVIATIONS

ACH = atypical complex hyperplasia
ASA = American Society of Anesthesiologists
ATN = acute tubular necrosis
BMI = body mass index
BSO = bilateral salpingo-oophorectomy
CI = confidence interval
EC = endometrial cancer
HYS = hysterectomy
LOS = length of stay
MI = myometrial invasion
OR = odds ratio
PLA = pelvic lymphadenectomy
RALH = robotic-assisted laparoscopic hysterectomy
UTI = urinary tract infection

TABLE 2

Perioperative findings and hospital course.

	HYS + BSO (N = 167)			HYS + BSO + PLA (N = 68[a])				Total (N = 235)		
	mean (SD)	median (IQR)	n (%)	mean (SD)	median (IQR)	n (%)	p-value	mean (SD)	median (IQR)	n (%)
Operative										
Intraoperative bleeding, ml	49 (58.9)			75 (59.8)			0.04[d]	57 (60.4)		
Conversion to open surgery			4 (2)			5 (7)				9 (4)
Skin to skin time, min.	106 (34.3)			165 (43.9)			< 0.001[d]	124 (45.7)		
Console time, min.	55 (16.3)			118 (38.8)			< 0.001[d]	72 (37.1)		
Lymph node count	–			25 (7.3)						
Technical breakdown with robot			1 (1)			3 (4)				4 (2)
Caused prolonged time in OR			1 (1)			2 (3)				3 (1)
Caused conversion			0			1 (1)				1(1)
Post-operative										
Diagnosis of endometrial cancer			144 (86)			67 (99)				211 (90)
Diagnosis of ACH			23 (14)			1 (1)[b]				24 (10)
Length of stay, days[c]		2.0 (1-3)			2.0 (2-3)		0.12[f]		2.0 (1-3)	
Readmission within 30 days			4 (2)			5 (7)	0.13[e]			9 (4)
Reoperation within 30 days			2 (1)			3 (4)	0.15[e]			5 (2)
Mortality within 90 days			0			0				0
Additional treatment										
Chemotherapy			4 (2)				4 (6)			8 (3)
Radiotherapy			3 (2)				0			3 (1)
Radiotherapy & chemotherapy			1 (1)				0			1 (< 1)

ACH = atypical complex hyperplasia; BSO = bilateral salpingo-oophorectomy; HYS = hysterectomy; IQR = interquartile range; OR = operating room; PLA = pelvic lymphadenectomy; SD = standard deviation.

a) 16 women in this group also had infracolic omentectomy.

b) This patient had ACH and a borderline ovary tumour I A. Lymph nodes were suspicious and therefore resected.

c) 1 woman was hospitalised for 119 days due to a coagulation defect. Excluding this outlier resulted in a range of 1-15 days.

d) Independent samples T test.

e) Fisher´s exact test.

f) Mann-Whitney U test.

The Danish Data Protection Agency (2007-58-0015/HeH.750.16-28) approved the study. According to Danish law, formal approval from The Danish National Committee on Biomedical Research Ethics System was unnecessary for this study. Likewise, the Danish Health and Medicines Authority did not find the study notifiable (3-3013-64/1/HKR).

Trial registration: not relevant.

RESULTS

We included 235 women with EC or ACH. Of these, 167 (71%) had a hysterectomy and a BSO; 68 (29%) had a hysterectomy, a BSO and PLA (**Table 1**). In all, 211 (90%) of the women were diagnosed with EC; 24 (10%) had ACH at final histology (**Table 2**). The women who did not have PLA had a significantly higher mean BMI than those who had PLA (Table 1). We found an overall conversion rate to open surgery of 4%. The reasons for conversion were enlarged uterus (n = 2), poor visibility (n = 1), adhesions (n = 4), technical difficulties (n = 1) and suspicion of ovarian malignancy (n = 1). The median LOS was two days. Overall 4% were readmitted (no differences between groups, p = 0.13). The reasons for readmission were ileus (n = 3), vaginal cuff infection (n = 1), vaginal bleeding (n = 1), wound infection (n = 1), urinary retention (n = 1), hernia (n = 1) and urinary infection (n = 1). Mean LOS for readmission was seven days (range: 1-16 days). The mean lymph node resection was 25 nodes, and two women had positive lymph nodes. No deaths occurred perioperatively or within 90 days post-operatively (Table 2).

The difference between women with and without PLA of having a Clavien-Dindo score of 3 or higher was (5% versus 9%) non-significant (p = 0.24) (**Table 3**). The risk of developing a grade 3 or higher grade complication was not significantly increased in the PLA group; odds ratio (OR) adjusted for cardiovascular disease and BMI was 2.14 kg/m^2 (95% confidence interval (CI): 0.68-6.71 kg/m^2; p = 0.19). A total of 21% (14/68) of the women developed lymphoedema that persisted for months after the surgery.

The overall incidence of one or more complications was 15% with no significant difference between those

TABLE 3

Complications according to the Clavien-Dindo scale. The values are n (%).

Grade[a]	HYS + BSO (N = 167)	HYS + BSO + PLA (N = 68[b])	Total (N = 235)
I	12 (7)	7 (10)	19 (8)
II	20 (12)	9 (13)	29 (12)
IIIa	1 (< 1)	2 (3)	3 (1)
IIIb	6 (4)	4 (6)	10 (4)
IVa	1 (<1)	0	1 (< 1)
IVb	0	0	0
V	0	0	0

BSO = bilateral salpingo-oophorectomy; HYS = hysterectomy; PLA = pelvic lymphadenectomy.
a) Definitions of grades: see Appendix.
b) 16 women also had infracolic omentectomy.

TABLE 4

Complications according to extent of surgery. The values are n (%).

Complication	HYS + BSO (N = 167)	HYS + BSO + PLA (N = 68[a])	p-value	Total (N = 235)
Intraoperative complications	0	0		0
Bleeding > 500 ml	0	0		0
30-day timeframe				
UTI	9 (5)	6 (9)		15 (6)
Pneumonia	0	1 (1)		1 (< 1)
Port site/wound infection	5 (3)	1 (1)		6 (3)
Vaginal cuff infection/ haematoma	3 (2)	2 (3)		5 (2)
DVT or PE	0	0		0
Stroke	0	0		0
Ileus	0	2 (3)		2 (1)
ATN	1 (< 1)	0		1 (< 1)
12-month timeframe				
Vaginal cuff dehiscence	3 (2)	1 (1)		4 (2)
Hernia	2 (1)	1 (1)		3 (1)
Vaginal prolapse	0	1 (1)		1 (< 1)
Total	23 (14)	15 (22)		38 (16)
≥ 1 complication	23 (14)	13 (19)[b]	0.32[c]	36 (15)

ATN = acute tubular necrosis; BSO = bilateral salpingo-oophorectomy; DVT = deep vein thrombosis; HYS = hysterectomy; PE = pulmonary embolism; PLA = radical pelvic lymphadenectomy; UTI = urinary tract infection.
a) 16 women also had infracolic omentectomy.
b) 2 women developed > 1 complication.
c) Fisher's exact test.

undergoing PLA and those who did not (14% versus 19%; p = 0.32) (**Table 4**). The OR for developing one or more complications for women having PLA adjusted for cardiovascular disease and BMI was 1.52 kg/m^2 (95% CI: 0.70-3.27 kg/m^2; p = 0.29). Two women having PLA developed more than one complication. The most frequent complication was urinary tract infection within 30 days of surgery, which occurred in 6% of the women; 3% developed a port-site infection or wound infection within 30 days (Table 4). Among the women who underwent PLA, 21% developed symptomatic lower extremity lymphoedema requiring compression stockings and physiotherapy during the first 12 months after surgery. The lymphoedema was stage 1 (n = 8), stage 2 (n = 3) and unknown stage (n = 3) according to the stages defined by the International Society of Lymphology.

DISCUSSION

The women included in this study were burdened with many of the known risk factors for EC: high age, obesity, hypertension and type 2 diabetes; and we found that 6% of the women developed a grade 3 or higher grade complication according to the Clavien-Dindo scale. In comparison, a recent larger study (n = 1,155) that pooled all gynaecological, oncological robotic surgery cases (n = 220) found a 7.8% incidence of grade 3 or higher grade complications [9]. Our incidence may be lower because of a different case mix as we only included women who had simple hysterectomy.

Our results are comparable to those of other studies of RALH for EC [10], but the complication rate is a higher than reported for benign cases treated by robotic surgery [9, 11]. The incidence identified in the present study is, however, similar to that observed for benign cases treated by laparoscopy [12]. The overall incidence of post-operative complications was 15% in our study in which no comparison with an alternative surgical method was made.

El Sahwi et al reported a 10% incidence of post-operative complications in a sample of RALH in comparison with 27% in an open surgery group [13]. Direct comparison is difficult because of the use of different definitions of complications, different case mixes, different lengths of follow-up and different methods for detecting complications. Hence, we recommend future registration of complications using the Clavien-Dindo system so that comparison can be made across populations and centres.

The Clavien-Dindo scale has the advantage of including any deviation from the normal post-operative course. The Clavien-Dindo scale is particularly relevant in retrospective analyses which involves a risk of post-operative problems being poorly reported in patient records. Using the Clavien-Dindo classification also prevents the use of poorly defined terms such as "major and minor" complications. It is a valid system for grading the severity of complications and has been proven to be both simple, comprehensive and reliable [8, 11]. The severity of complications is important both from a patient, a clinical and a socioeconomic perspective.

Our study showed no significant difference in the incidence of grade 3 or higher complications between women undergoing PLA and those who did not. Nor did the former develop more overall complications or have a longer LOS than the latter. This contrasts with previous

studies reporting that lymphadenectomy increases the risk of post-operative morbidity and increases costs [14]. The lack of a significant difference between the groups in our study may be related to the fact that complications are rare or that our sample may be too small (type 2 error).

Readmissions are a measure of the quality of care and are also important in a socioeconomic perspective. We found a readmission rate of 4% within 30 days with no significant difference between women with or without PLA. The mean LOS for readmission was seven days. It has previously been reported that the rate of readmissions after robotic surgery for EC was 7.6% within three months and that the mean readmission LOS was 2.5 days [15]. The incidence of vaginal cuff dehiscence was 2% and dehiscence occurred either during coitus or spontaneously. Vaginal cuff dehiscence has been reported to occur from three days up to 30 years after surgery [16], and any dehiscence requires prompt surgical intervention. Vaginal cuff dehiscence is a known, but rare and unpleasant complication to hysterectomy and has been reported long before robotic surgery was introduced. It has, however, been suggested that robotic surgery may be associated with a higher incidence of dehiscence [16].

The incidence reported in the present study is comparable to those reported in similar studies on robotic surgery (varying 0.4-1.5%) [17, 18]. Possible causes of vaginal cuff dehiscence are thermal injury or insufficient suturing technique, which may be due to the magnification or the surgeon lacking tactile feedback. Increased age, previous vaginal surgeries, vaginal atrophy and factors associated with poor wound healing (malignancy, radiation), post-operative vaginal cuff infection and haematoma may also be risk factors [16]. The women in the present study were advised to postpone their first intercourse until eight weeks after RALH to reduce the risk of vaginal cuff dehiscence.

Nevertheless, vaginal cuff dehiscence occurred more than nine months post-operatively in one case. Fourteen (21%) of the women who underwent PLA developed symptomatic lower extremity lymphoedema within 12 months post-operatively – a condition that may persist throughout life. We defined lymphoedema as being present when the gynaecologist referred a woman to physiotherapeutic examination and treatment. Here the stage of lymphoedema was assessed and treatment given. Lymphoedema occurs after various surgical approaches. In a large evaluation of 1,298 women who were treated for EC, the overall incidence was 3.4% after more than ten lymph nodes were removed [19]. Our incidence of lymphoedema was higher than that reported in other robotic studies which may be due to our definition of lymphoedema. A large study

Robotic-assisted laparoscopic hysterectomy at Herlev Hospital.

of 471 women treated with RALH reported a 13.4% incidence of lymphoedema with a median of 25 months follow-up [18]. Different observation periods and defining criteria for lymphoedema may explain the different findings across studies. There is evidence that lymphoedema typically develops within the first post-operative year [20]. We therefore recommend that patients be followed for a minimum of 12 months post-operatively for lymphoedema. Additionally, further implementation of the sentinel node technique in the surgical treatment of EC will, hopefully, reduce the risk of this disability and associated morbidity.

A strength of this study is the use of the Clavien-Dindo scale, a validated tool for exploring retrospective data [8] and for comparing post-operative complications across studies. Another strength is the use of two assessors and an arbitrator to obtain valid data. The study has inherent limitations due to its retrospective design, reliance on data from hospital charts and the lack of a control group undergoing transabdominal hysterectomy or laparoscopic hysterectomy.

CONCLUSION

This retrospective descriptive study showed that approximately 6% of women with early stage EC or ACH developed post-operative grade 3 or higher grade complications after RALH according to the Clavien-Dindo scale. This indicates that RALH is safe and well-tolerated in women with early-stage EC.

As more women are being treated with RALH worldwide and the indication for robotic surgery is widening to include more obese women and women with more co-morbidity, it is relevant to closely monitor the quality and safety of this technique in regard to post-operative complications. We recommend using the Clavien-Dindo scale to allow comparison across populations.

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APPENDIX

Classification of surgical complications – The Clavien-Dindo scale [8].

Grade	Definition
I	Any deviation from the normal post-operative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions Allowed therapeutic regiments are: drugs as antiemetics, antipyretics, analgesics, diuretics, electrolytes, and physiotherapy This grade also includes wound infections opened at the bedside
II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications Blood transfusions and total parenteral nutrition are also included
III	Requiring surgical, endoscopic or radiological intervention
IIIa	Intervention not under general anaesthesia
IIIb	Intervention under general anaesthesia
IV	Life-threatening complications (including CNS complications)[a] requiring IC/ICU management
IVa	Single-organ dysfunction (including dialysis)
IVb	Multiorgan dysfunction
V	Death of a patient
Suffix "d"	If the patient suffers from a complication at the time of discharge, the suffix "d" (for "disability") is added to the respective grade of complication This label indicates the need for a follow-up to fully evaluate the complication

CNS = central nervous system; IC = intermediate care; ICU = intensive care unit.
a) Brain haemorrhage, ischaemic stroke, subarachnoid bleeding, but excluding transient ischaemic attacks.

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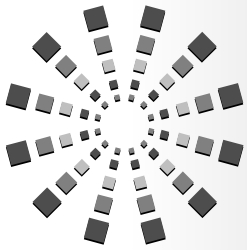

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The Experience of Robotic-Assisted Laparoscopic Hysterectomy for Women Treated for Early-Stage Endometrial Cancer

A Qualitative Study

KEY WORDS
Content analysis
Endometrial cancer
Patient experience
Qualitative research
Robotic-assisted laparoscopic hysterectomy

Background: An increasing number of women are offered robotic-assisted laparoscopic hysterectomy as treatment for early-stage endometrial cancer in the developed world. **Objective:** The aim of this study was to explore how women diagnosed with early-stage endometrial cancer experienced robotic-assisted laparoscopic hysterectomy. **Methods:** Semistructured interviews were carried out with 12 women, and interview data were analyzed by qualitative content analysis. **Results:** Four overarching themes emerged: ''surgery was a piece of cake,'' ''recovering physically after surgery,'' ''going from being off guard to being on guard,'' and ''preparing oneself by seeking information.'' The women had confidence in the robotic technique and experienced fast recovery after robotic-assisted laparoscopic hysterectomy; however, they had uncertainties and unanswered questions concerning the postoperative course. Shortly after discharge, the women did not consider themselves surviving cancer patients but as cured. The women searched for information from various sources, for example, the Internet and the online patient chart, to prepare for surgery and to come to terms with the diagnosis. **Conclusions:** Although the women had confidence in the robotic technique and recovered quickly physically, they lacked information about what went on in the operation theatre and about their new anatomy. **Implications for Practice:** Patient education about the normal postoperative course in regard to

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vaginal bleeding, bowel function, and level of physical activity is needed. Individualized information about anatomical changes after surgery is warranted, preferably using anatomical drawings. Potentially, the women could benefit from attending a nursing clinic during the first postoperative months.

In Denmark and many other parts of the developed world, an increasing number of women are offered robotic-assisted laparoscopic hysterectomy as treatment for early-stage endometrial cancer. How women feel about this robotic surgical treatment has, to our knowledge, not previously been explored. Knowledge of how they react physically and mentally to robotic surgery and how they experience the disease and treatment trajectory could inform healthcare professionals and support them in giving appropriate information about treatment and potential short- and long-term adverse effects. Because of the short length of hospital stay and limited contact in the outpatient clinic, healthcare professionals have only brief contact with these women. Knowledge of the patient perspective is therefore imperative for healthcare professionals to provide relevant information and nursing care and to decrease patient distress.

Endometrial cancer is the most common cancer in the female genital tract in the developed world with an incidence between 11 and 20 per 100 000 women.[1] It predominantly occurs in postmenopausal women.[1,2] The most important risk factors for endometrial cancer are increasing age, obesity, and physical inactivity.[2] Approximately 80% of patients are diagnosed in stage I,[2] and the overall 5-year survival rate of all stages is 80% in developed countries.[1] Endometrial cancer is primarily treated surgically with hysterectomy, bilateral salpingo-oophorectomy,[3] and in high-risk cases pelvic lymphadenectomy and omentectomy.[2] In Denmark, robotic-assisted laparoscopic hysterectomy has been a treatment option for women with endometrial cancer since 2008.

Knowledge of how women experience robotic-assisted laparoscopic hysterectomy may help to optimize and target the care of women both preoperatively and postoperatively. Consequently, the aim of this study was to investigate how women diagnosed with early-stage endometrial cancer experienced robotic-assisted laparoscopic hysterectomy.

■ Methods

This was a qualitative study using content analysis as described by Graneheim and Lundman.[4] Content analysis is a research method that provides a flexible and pragmatic way to develop new knowledge and understanding of a phenomenon. The method focuses on the characteristics of language as communication with attention to the content or contextual meaning of the text.[5] It is a subjective interpretation of the data through the systematic classification process of coding and identifying themes or patterns. Content analysis may cover a manifest or latent content. The obvious and visible content of the texts is labeled manifest, whereas the text involving interpretation of the underlying meaning is considered latent.[5] Content analysis is usually appropriate when existing theory or research literature on a phenomenon is limited. The rationale for using this method is to avoid using preconceived categories.[5] We used an inductive category development,[4] which allows categories to flow from data rather than from theory or prior research.

The study was approved by the Danish Data Protection Agency (HEH 750.16–27). According to Danish law, formal approval from the local ethical committee was not necessary. The committee was notified of the study and found further formal appraisal of the study unnecessary (H-4-2013-177). All women signed a consent form prior to the interviews after receiving oral and written information about the study. The interviewer was not involved in the care or treatment of informants. Informants were notified that they could be referred to clinical staff if they experienced distress or needed additional information after participating in the interview.

Data Collection

We collected data using individual semistructured interviews of women treated with robotic-assisted laparoscopic hysterectomy for early-stage endometrial cancer. We developed an interview guide prior to the interviews, which was evaluated and aligned after the first 2 interviews. All interviews were initiated with the following question: "Please tell me how you experienced the course of your treatment and illness?" (Table 1). Response validation was conducted during interviews. Interviews were recorded digitally and subsequently transcribed verbatim by a study team member according to a transcription protocol. The transcribed length of all interviews was 194 full pages. Audit trail memos[6] were made after interviewing and after transcription. We judged that data saturation was achieved after interviewing 12 women. The same team member conducted all interviews either at the hospital or at the informants' home as preferred by the women. Recruitment of women included women with and without postoperative complications (demanding treatment), women living alone and cohabiting, and women employed and retired (Table 2). A criterion sample[6] was obtained. Inclusion criteria were as follows: endometrial cancer at the final histology, treated by robotic-assisted laparoscopic hysterectomy, and sufficient language proficiency. Women needing adjuvant treatment were not included as this treatment could move focus from the surgical treatment. The interviews were conducted between 6 and 19 weeks after surgery (mean, 12 weeks). The interviews lasted between 59 and 92 minutes (mean, 75 minutes).

Informants

The first author had prior contact with informants as she included women in an ongoing prospective cohort study of

Table 1 • Interview Guide

1. Please tell me how you experienced the course of your treatment and illness.
2. What did you know about robotic surgery before your operation?
3. What thoughts went through your head when you were told you were going to be operated robotic assisted?
4. How did you experience the robotic-assisted surgery?
5. What would you say to a friend who was about to go through the same surgery you have been through?
6. What was it like to be ill?
7. Is there anything you would like to add to your story?

postoperative complications and quality of life. She contacted potential informants by telephone. A total of 15 women were approached and asked to participate; 12 consented. Reasons for not wanting to participate were not having time (n = 2) or wanting to forget the experience (n = 1). Characteristics of study informants are described in Table 2.

Data Analysis

Interview data were analyzed using the 5 steps described by Graneheim and Lundman.[4] First, 2 study team members read all interviews to achieve immersion and a sense of whole; 2 other team members read a couple of interviews to get a sense of the material. Second, data were divided into meaning units, condensed and labeled with a code by 1 team member, and subsequently confirmed by another member. Third, 1 team member compared codes (differences and similarities) and sorted codes into categories and confirmed them with another member. The tentative categories comprised the manifest content. Fourth, 2 team members discussed and revised the tentative categories. Finally, the latent content of the categories was condensed into themes; the latter were confirmed by all authors.[4] QRS Nvivo 10 software (QRS International Pty Ltd, Victoria, Australia, 1999–2012) was used for data analysis.

Trustworthiness

In a qualitative study, trustworthiness must be addressed[7,8] and includes credibility, conformability, dependability, and transferability.[9] To achieve credibility, the sample was recruited using criterion sampling in an effort to capture sufficient data to account for variation in the women's experiences (Table 2).

Table 2 • Characteristics of Informants (n = 12)

	n	Range	Mean
Age, y	12	51–76	63
Living alone	6		
Employed	6		
Time since surgery, wk		6–19	12
Pelvic lymphadenectomy	3		
Women without complications	8		
Complications demanding treatment[a]			
Lymphedema	1		
Hematoma	2		
Urinary tract infection	2		
Strong psychological reaction	1		

[a]Two women had 2 types of complications.

Variation in the sample also increased transferability. The stringent analytical process and the fact that 4 team members with different clinical perspectives and distance analyzed the data support the credibility and dependability of the study. Audit trails as memos after interviews served to strengthen dependability. Generalization is not the aim of qualitative research, but the individual reader must decide whether the findings are transferrable to a specific context.[10,11]

■ Results

Characteristics of informants are shown in Table 2. Analysis of data resulted in the following 4 major themes: (1) "robotic surgery was a piece of cake," (2) "recovering physically after surgery," (3) "going from being off guard to being on guard," and (4) "preparing oneself by seeking information" (for underlying categories, see Figure).

Robotic Surgery Was a Piece of Cake

The women had limited preoperative knowledge of the robotic technique but had faith in the robotic surgeons. The women were convinced that they got the most up-to-date treatment available and grateful for that. Staff were regarded as optimistic and positive in their attitude toward robotic surgery, and their attitude was adopted by patients. The keyhole approach was appealing to the women as they were aware of the shorter postoperative recovery time and decreased risk of infection compared with open surgery. They considered the robotic approach as being state of the art but at the same time mysterious because they did not fully comprehend how the surgery was actually performed. The technical approach seemed to minimize the women's fear of any human errors occurring during surgery, and technical breakdown was considered an unfortunate possibility, but faith in the safety of the robotic technique was overall strong, and reservations were few. One woman speculated that the robotic technique entailed a physical distance between her and the operating surgeon sitting behind the console and worried that the surgeon might not be able to acknowledge if something went wrong during surgery. The loss of tactile feedback for surgeons was also a concern, although a minor one. The women attributed positive outcomes to the robotic surgery. One woman expressed relief because the technique prevented the surgeon from forgetting any instruments inside her. Another woman reported being certain that the 3-dimensional visualization during surgery would enable the

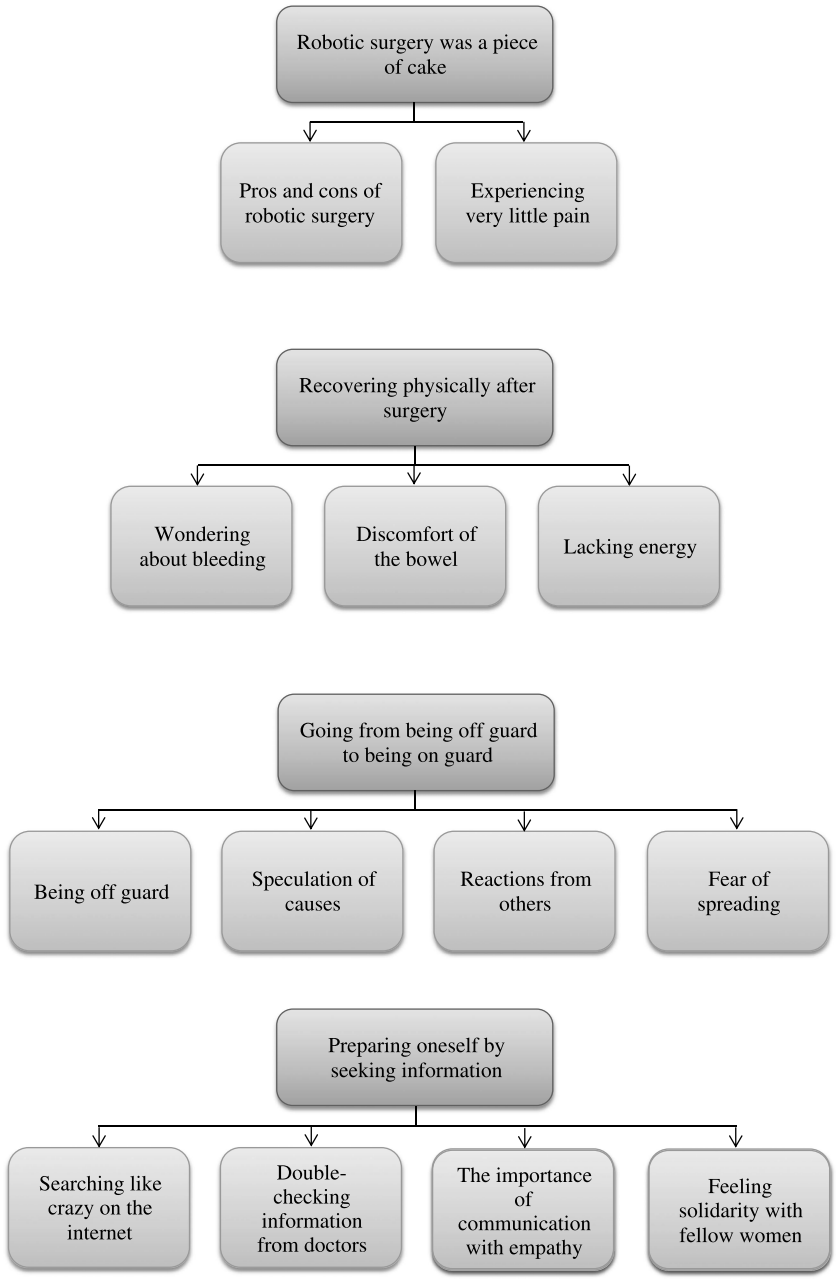

Figure ■ Themes and categories.

surgeon to find all the cancer tissue, reassuring her that the search for cancer in her body had been comprehensive.

> I don't think you should fear this [robotic surgery]; you should just surrender, let go; it [robotic surgery] is so precise, it is so… considering they are removing an organ, from inside of you, then it is just so precise. It is incredible that it is possible and that it doesn't affect your well-being more. (Informant 7)

The women were surprised that they experienced so little pain postoperatively. They had anticipated pain, but abdominal pain and pain from port sites were described more as a discomfort that resolved after a few days or weeks. Pain and a sense of pelvic discomfort were interpreted by the women as a symptom of doing too much physically, either returning too soon to physically demanding work, not resting enough during the day, or working too hard in the house or in the garden.

The women were nervous prior to surgery; however, postoperatively they experienced a rapid recovery. Prior to surgery, the women were informed of the risk of perioperative and postoperative complications. Postoperative complications, for instance, lymphedema or urinary tract infections, did occur (Table 2) and were a source of concern for the women affected. They nevertheless maintained an overall positive attitude.

> I know it sounds crazy to say this afterward, but in hindsight, it [the robotic operation] was a piece of cake. (Informant 10)

Recovering Physically After Surgery

After discharge from the hospital, the women were in doubt what to regard as normal bodily functions. Bleeding, bowel function, and tiredness were the predominant concerns. The women were unsure how much vaginal bleeding to expect, and consequently, they were uncertain when or whether to contact the hospital. Looking back, they were surprised how little vaginal bleeding they experienced postoperatively, and some worried that this might be abnormal. Others had more vaginal bleeding during a long period of time postoperatively and were likewise unsure how or whether they should react. Although postoperative vaginal bleeding is normal and expected after robotic-assisted laparoscopic hysterectomy, some women did not associate vaginal bleeding with the surgery itself. Rather, they speculated whether it was a sign of infection or of the cancer still being there, or in fact, if the cancer had spread. Because several women had experienced bleeding as the first symptom of disease, some automatically associated bleeding with "cancer," and postoperative bleeding therefore rekindled their fear. Bleeding was an overall concern, and the women felt unprepared for the worry that vaginal bleeding or lack of vaginal bleeding caused after discharge.

> At some point I thought, I wonder if I should call them [hospital staff] and tell them I am not bleeding at all? Then again I thought… I'd better not (whispers). (Informant 3)

> I've worried a lot about the bleeding because it was how it [the cancer] all started! (Informant 11)

Postoperatively, painful defecation was unexpected and troubling. Constipation was prevalent. The women were careful not to press too much postoperatively because they were afraid of causing internal damage. They were generally unsure of how long they should continue to use stool softeners and laxatives. Abdominal bloating was common, unpleasant, and, as some women reported, continued several weeks after surgery. Several women considered constipation and bloating to be the worst physical adverse effect of the surgery.

> The first times I went to the bathroom I thought, "I'm going to faint! I was in so much pain… I thought, 'Oh, is it going to be like this from now on?'" I can't stand it! Luckily it is only once a day. Anyway, I felt a little better as the days went by, and suddenly I realized I wasn't afraid of going to the toilet anymore. It was a surprise that it could be so painful. I have had so much gas for 4 weeks. Four weeks! I wouldn't have thought it would be like this. (Informant 2)

There was an awareness of the importance of being active after discharge and a will to adhere to instructions from hospital staff about physical activity. The dilemma was to be active and regain one's normal level of activity on the one hand and on the other hand, to be careful not to be too active and provoke internal injury. This dilemma raised questions: on the one side, the women were astonished by their rapid recovery; on the other side, they were surprised by the significant lack of energy they experienced after having minimally invasive surgery and so short a hospital stay.

> The most surprising fact has been how little energy I've had. I kept thinking now it [the operation] is over, I must get my energy back. But it hasn't been like that. I have great moments… when I have the energy to go to town, but the next day… it catches up with me, and I'm dead (laughs). (Informant 11).

Some women associated their overwhelming postoperative tiredness with the anesthesia.

> I could feel it when I went on my walks, I needed to recover. I was weak, although it is a short experience [the operation], 3 hours and the anesthesia and home the very next day. But there is a lack of energy in your body I have never experienced before. You feel very tired and weak. (Informant 3)

Going From Being Off Guard to Being On Guard

The women felt they were caught by surprise by the endometrial cancer diagnosis. In other words, they felt they had been "completely off guard" in regard to anything being seriously wrong. Most of the women had initially experienced vague symptoms and were taken aback by their hasty referral to the hospital. They were concerned that because their symptoms had been vague, the endometrial cancer could actually have gone undetected for a long time. The women were comforted by doctors who assured them that endometrial cancer has favorable survival rates and as such could be considered the "best" place in the female reproductive tract to have a cancer. Endometrial cancer is mostly diagnosed at an early stage because of the initial symptom of postmenopausal bleeding, which prompts the women to consult their general practitioner.

> It is the best place [in the uterus] to have a cancer, if you must. Your body will let you know! (Informant 8)

All the women wondered about the cause of their cancer. They knew that early menarche, late menopause, and a high production of estrogen were risk factors for endometrial cancer. One woman speculated that her sedentary lifestyle could have been a risk factor. Generally, they concluded that the cancer was not self-inflicted but merely a result of chance or of chemical reactions in the body.

> …it does not have anything to do with your diet, it's hormones. So you can't do anything. It's all down to chemical processes in the body; we can't help it. I don't think we can help it. I didn't think I produced much estrogen as I've had a hard time getting pregnant. (Informant 12).

The women moved on during the weeks after surgery and after receiving the final diagnosis. They did not consider themselves to be cancer survivors. However, they experienced that friends, family, and remote acquaintances reacted with sadness to their cancer diagnosis, a reaction the women considered unnecessary.

> Now I feel great, and it feels wrong when people ask, "Where have you been?" and I say, "I went to have surgery because of endometrial cancer." They become

very disturbed and frightened. I feel sorry for them as I don't feel the same fear any more. I don't feel like a cancer patient or anything like that. (Informant 10)

Some women received compensation for critical illness from their insurance company. Some felt unworthy of this as they considered themselves cured. Despite this, they nevertheless sought reassurance from healthcare professionals that they were in fact cured after surgery. After getting back to normal, some women feared metastasis or recurrence of the cancer. They were disturbed when they experienced vaginal bleeding, pain from the bladder, or even a sore throat. They feared the symptoms were due to recurrence of their cancer, and they were constantly on guard.

I can't help thinking about it; you live a little on a ticking bomb. When will it come back? And where? (Informant 12)

The new anatomy was in general a bit unclear to the women, but they did not proactively clarify this. Prior to surgery, surgeons explained which organs from the female genital tract would be removed and that the top of the vagina would be sealed by stitches. Nevertheless, after surgery, the women remained uncertain of whether their cervix was still there and whether they would still need to go for smear tests. Logically, it was hard for some to imagine recurrence when indeed the uterus, fallopian tubes, and ovaries were removed. However, the women found the follow-up visits at the hospital for 3 years after surgery reassuring.

Preparing Oneself by Seeking Information

Prior to surgery, the women described being highly anxious, including having some irrational thoughts and a focus on worst possible outcomes. They sought information from multiple different sources: healthcare professionals, the Internet, and family or friends who might have had any experiences. Information helped them and their relatives prepare and helped them understand and to some extent come to terms with the situation. Several women expressed a preference for more technical and medical information about the robotic surgery itself in order to be more prepared for activities in the operating room before and after the robotic surgery.

I didn't know how you were positioned in the operating room and stuff like that. (Informant 5)

When receiving the histology report 1 week after surgery, the women and their relatives wanted as much information as possible (ie, size in millimeters and position of the tumor in the uterus) so they could picture the tumor and the threat they had been facing. During consultations with doctors, the women were alert to potential threats, and they tried hard to understand all the medical facts in order to achieve a sense of control.

Most of the women had access to the Internet and had used it prior to surgery to get more information, primarily about endometrial cancer and secondly about robotic surgery. The women wanted to know if they could have done something to prevent the cancer, and they also sought information about the prognosis. Information was reassuring and troubling, the latter because accessible information was general and therefore not necessarily directly applicable.

I was on the Internet almost constantly (laughs) to gain control and find information. (Informant 12)

Today there is no doubt; you go on the Internet to read stuff. I have chosen not to do this after [the surgery], I did it before. My choice was good and bad. You tend to focus on the negative, if you don't have the verbal explanations… you question the credibility of what you read. (Informant 9)

The majority of women accessed their online patient charts postoperatively to get additional information and to gain reassurance, although they did not always fully comprehend the medical language. They were specifically interested in the description of the surgical procedure and the histology results. They compared the written and verbal information from doctors to see if the 2 concurred and to check that no information had been withheld.

It takes a little time [before you can access your patient record online]… but it was great to read the pathology report, to read they had examined it [the uterus] from right to left, and there was no dissemination and all that. It was great. (Informant 10).

Generally, the women felt they had received relevant verbal information from doctors and nurses. However, they stressed that for doctors it may be routine to provide information about a cancer diagnosis, but for the patient, it was certainly not routine to receive such a diagnosis.

I needed her [the gynecologist] to repeat it [the diagnose of endometrial cancer] a couple of times, so I could come to terms with the diagnosis. She was a bit unsympathetic toward this. She asked if I didn't know this was what it was all about. (Informant 3)

The women discussed the false security they had felt from attending the cervical smear program and getting negative results. Discovering another cancer in the female genital tract despite a negative smear was perplexing. Generally, they thought that the cervical smear covered the entire female genital tract.

The women noted that there was sparse public knowledge available about endometrial cancer and its initial symptoms. Based on their personal experience, they felt compelled to take it upon themselves to inform and warn other women to react at once to postmenopausal bleeding.

■ Discussion

The aim of this study was to investigate how women diagnosed with early-stage endometrial cancer experienced robotic-assisted laparoscopic hysterectomy. The major themes found were "surgery was a piece of cake," "recovering physically after surgery," "going from being off guard to being on guard," and "preparing oneself by seeking information." The women primarily focused on their

life situation after being diagnosed with endometrial cancer and the potential threat this posed to their life. In comparison, the robotic surgical approach and their experience of this were of secondary concern. This finding concurs with a phenomenological study of the same population,[12] where the experience of undergoing laparoscopic hysterectomy was explored.

Confidence in the robotic technique was adopted from hospital staff, and the women had few concerns about the technique, even those who developed postoperative complications that merited treatment. Previous studies in gynecology[12,13] have reported that women have overall trust in doctors and other healthcare professionals and consider the surgeon to have the expert skills and knowledge of the best treatment action. In a qualitative study of cancer patients (not gynecologic), faith in doctors reflected an understanding of the complexity and the medical uncertainty of cancer and its treatment.[14] Similarly, the women in the present study realized the complexity and medical uncertainties of their endometrial cancer. Hence, they gave up attempting to understand the robotic technique and instead considered it the doctors' domain. The women had overriding faith in doctors and the robotic treatment. All the women in this study were informed prior to surgery about known potential adverse effects of robotic surgery and the risk of conversion to open surgery. In a previous study, it was found that women who were cautioned of complications or adverse effects before surgery accepted complications more easily.[13]

It has been theorized that individuals construct commonsense models to define and construct their illness experience and at the same time to guide health behavior.[15,16] Leventhal's self-regulatory model of illness cognition[15,17] explains how individuals have certain illness cognitions or illness beliefs and subsequently follow specific patterns to resume normality. Leventhal describes how the individual is confronted with symptom perception (in this study vague symptoms, often vaginal bleeding) and social messages (the doctor informs about the preliminary diagnosis of endometrial cancer). At this stage, illness cognition develops involving the dimensions: identity (symptoms), cause, consequences, timeline (how long it will last), and cure/control (beliefs of cure/control). In the present study, the women sought information about why they had developed cancer, with the majority reaching the conclusion that it was not self-inflicted but induced by hormones or merely by chance. Only 1 woman speculated that her sedentary lifestyle could have been a risk factor. According to Leventhal, emotional responses to the health threat may be fear, anxiety, and depression.[15] In the present study, the women were distressed by the tentative cancer diagnosis prior to surgery. Some could not stop seeking information, whereas others reacted by not seeking external information at all. Leventhal's theory posits that a strong illness identity may be related to the belief that the illness entails serious consequences and will last for a long time.[15] In the present study, the women did not see themselves as cancer survivors. Rather, they expressed that family and friends reacted with inappropriate sadness to their cancer diagnosis. This could be due to a weak illness identity resulting from the women's hasty referral to treatment within a time span of weeks and the fact that none of these women were referred to adjuvant treatment.

In the present study, the women were initially caught off guard by their illness. When their symptoms turned out to be due to a cancer, some women reacted by feeling vulnerable and relying heavily on healthcare professionals to identify any recurrence. The illness representation developed by the women was that endometrial cancer was an illness without clear warning signals, an "invisible" or "silent" disease. Consequently, the women depended on reassurance from medical staff in terms of medical examinations, confirming that they were indeed free of disease and cured. That medical reassurance reduces the fear of cancer recurrence has been previously reported.[16] Similarly, the women in this study were reassured by the prospect of attending follow-up visits for 3 years after surgery.

Overall, recovery after the robotic surgery was experienced as easy and rapid. The women were nevertheless puzzled by the fact that so short a hospital stay and minimally invasive surgery could induce so much weakness and tiredness for days and weeks postoperatively. The women needed individually tailored information about when they could resume their normal activities. Some experienced comorbidities and a low level of function, whereas others were normally very active, for example, with horseback riding, fitness, and other strenuous sports. The concern not to create internal damage seemed to be universal regardless of the individual woman's habitual level of physical activity. Therefore, individually tailored information about how to remain active and at the same time not overdo is required.

In addition to lack of energy and tiredness, the women had discomfort of the bowels. Constipation, sense of bloating lasting several weeks, and painful defecation appeared to be the worst adverse effect of the robotic surgery. Similar findings were reported in a study of women who had a hysterectomy openly or laparoscopically.[13] The women in the present study were uncertain of how to dose stool softeners and laxatives and for how long they should take them. Our findings indicate a need for individualized instructions on how to cope with postoperative lack of energy and how to administer laxatives during the first weeks after surgery.

Vaginal bleeding was another source of worry and uncertainty despite it being a normal and well-known postoperative occurrence. The women were unsure about how much or little vaginal bleeding to expect. Robotic surgery is known to induce minimal bleeding during surgery.[18–20] In the present study, most women experienced minimal or no bleeding postoperatively. This was surprising for many and disturbing for some and was a cause of uncertainty in regard to if or when they should contact the hospital. It has previously been found that bleeding after hysterectomy can be perceived as loss of control.[12] It appears essential that women undergoing robotic-assisted hysterectomy are informed of the reasons for and the time range and amount of postoperative bleeding to expect postoperatively.

The need for information differed from woman to woman. There was a general need for more specific information about the procedure in the operating theater. During consultations with doctors, some women strived to understand all the medical facts in an effort to gain control and reduce anxiety. Opposed to this, Leydon and colleagues[14] in a qualitative study of 17 patients diagnosed with different cancer illnesses concluded that a coping

strategy to regain hope could be to not seek information. They found that fear affected the wish for information and that cancer patients could be ambivalent regarding the amount and level of detail they preferred.[14] A previous study found that younger age, higher educational level, more recent diagnosis, having undergone radiotherapy, absence of comorbidities, having a partner, and having received written information were factors associated with a higher perceived level of information.[21] The women in the present study appeared well educated and resourceful, which could explain their need for a high level of information. Seeking information on the Internet was another way to empower oneself and gain information in order to be able to ask specific questions and prepare for adverse effects and prognosis. This concurs with the findings of a qualitative study of 20 cancer patients who were interviewed about their experiences of using the Internet for information.[22] Information on the Internet was both in lay and medical language but not patient specific. Information in the online record, on the other hand, was patient specific but written in medical terms, making it difficult for the women to fully comprehend the content.

In general, the women appeared uncertain of their anatomy both preoperatively and postoperatively, for example, being surprised that the cervix smear could not detect endometrial cancer. This is similar to findings in other studies.[13,23] In addition, the women in the present study did not ask healthcare professionals to clarify uncertainties about their new anatomy. To ensure the women's understanding of the changes to their female anatomy following robotic-assisted laparoscopic hysterectomy, preoperative information about the changes should be repeated postoperatively, preferably using graphical illustrations.

The women in the present study were overall taken aback by the lack of public knowledge of endometrial cancer, including the initial symptoms of the disease. In the immediate postoperative period, they felt compelled to take it upon themselves to warn fellow women. As the incidence of endometrial cancer is expected to increase over the next years because of an aging population and a growing number of obese people in Denmark, an information campaign targeting this disease might be appropriate. Screening is not an option for detecting uterine hyperplasia or cancer because of insufficient sensitivity and specificity.[24] Awareness of the initial symptoms of endometrial cancer must therefore begin with the women themselves and with the general practitioner taking immediate action.

Strengths and Limitations of the Study

A strength of this study is that it has been reported according to the COREQ 32-item checklist[25] for all relevant items. It may be both an advantage and a disadvantage that the interviewer had contact with the women prior to conducting the interviews. The interviewer was hospital employed and also recruited the women for an ongoing prospective study of postoperative complications and quality of life after robotic surgery. It is possible that this resulted in informants being influenced by social desirability, making them reluctant to overtly critique the robotic procedure in fear of later consequences or in order to please the interviewer. On the other hand, knowing each other from an earlier study could facilitate trust and communication during interviews. An important limitation is the sampling of women from an ongoing prospective study. The women who agreed to participate in the prospective study are likely already selected in the sense that they are resourceful and have the energy and strength to participate in studies. This could explain why our results differ in some areas from other studies.

■ Conclusions

Overall, the women had confidence and trust in surgeons and the robotic technique. Shortly after discharge, the women did not have a strong illness perception and hence did not consider themselves to be cancer survivors. Despite this, they nevertheless feared dissemination of the cancer perhaps because initial symptoms of endometrial cancer were vague. The vagueness of initial symptoms had caught them off guard. However, following diagnosis and surgery, they were now constantly on guard for fear of disease recurrence. The women felt informed about the risk of complications, but remained uncertain about the normal postoperative course of vaginal bleeding. Postoperatively, physical changes were considered minimal, and recovery was rapid with the exception of prolonged bowel discomfort and tiredness. The women preferred as much information as possible as this gave them a sense of empowerment.

It is reassuring that this patient group appears to have complete confidence in the robotic technique. However, concrete information about, for example, positioning and roles of healthcare staff during the actual robotic procedure, is warranted. Changes in anatomy after surgery could also be visualized in anatomic drawings that the women can take home after discharge. Information about changes in anatomy may also be repeated at scheduled follow-ups visits. Patient education about the normal postoperative course in regard to vaginal bleeding, bowel function, and level of physical activity is needed in order to minimize postoperative concerns and complications. This patient population could potentially benefit from attending a nursing clinic during the first postoperative months. In a broader healthcare perspective, a campaign encouraging postmenopausal women to react promptly to vaginal bleeding and seek medical attention might enhance awareness of the symptoms of endometrial cancer.

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AOGS
ACTA Obstetricia et Gynecologica Scandinavica

AOGS ORIGINAL RESEARCH ARTICLE

Cost-analysis of robotic-assisted laparoscopic hysterectomy versus total abdominal hysterectomy for women with endometrial cancer and atypical complex hyperplasia

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Key words
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Abstract

Introduction. The aim was to analyse the hospital cost of treatment with robotic-assisted laparoscopic hysterectomy and total abdominal hysterectomy for women with endometrial cancer or atypical complex hyperplasia and to identify differences in resource use and cost. *Material and methods.* This cost analysis was based on two cohorts: women treated with robotic-assisted laparoscopic hysterectomy (n = 202) or with total abdominal hysterectomy (n = 158) at Copenhagen University Hospital, Herlev, Denmark. We conducted an activity-based costing analysis including consumables and healthcare professionals' salaries. As cost-drivers we included severe complications, duration of surgery, anesthesia and stay at the post-anesthetic care unit as well as number of hospital bed-days. Ordinary least-squares regression was used to explore the cost variation. The primary outcome was cost difference in Danish kroner between total abdominal hysterectomy and robotic-assisted laparoscopic hysterectomy. *Results.* The average cost of consumables was 12 642 Danish kroner more expensive per patient for robotic-assisted laparoscopic hysterectomy than for total abdominal hysterectomy (2014 price level: 1€ = 7.50 Danish kroner). When including all cost-drivers the analysis showed that the robotic-assisted laparoscopic hysterectomy procedure was 9386 Danish kroner (17%) cheaper than the total abdominal hysterectomy (p = 0.003). When the robot investment was included, the cost difference reduced to 4053 Danish kroner (robotic-assisted laparoscopic hysterectomy was 7% cheaper than total abdominal hysterectomy) (p = 0.20). Increasing age and Type 2 diabetes appeared to influence the overall costs. *Conclusion.* For women with endometrial cancer or atypical complex hyperplasia, robotic-assisted laparoscopic hysterectomy was cheaper than total abdominal hysterectomy, mostly due to fewer complications and shorter length of hospital stay.

Abbreviations: ABC, activity-based costing; ACH, atypical complex hyperplasia; BSO, bilateral salpingo-oophorectomy; CI, confidence intervals; DKK, Danish kroner; DRG, Diagnosis-Related Group; HYS, hysterectomy; OM, omentectomy; PACU, post-anesthetic care unit; PLA, pelvic lymphadenectomy; RALH, robotic-assisted laparoscopic hysterectomy; TAH, total abdominal hysterectomy.

Introduction

Most health care systems strive to produce high quality health care with an efficient use of resources. Improvements in efficiency can be achieved when a certain amount and quality of health care can be produced with use of fewer resources or lower costs. Assessments of efficiency require reliable analyses of the resources used and associated costs. Hospital accounting systems traditionally consider the cost of input factors and are generally not suitable for detailed assessment of efficiency in resource utilization because they do not relate the input of resource to the production of health care. Activity-based costing (ABC) is a method that is suitable for the assessment of resource use required for a particular production process (1). The ABC method breaks down the treatment process into activities that are clinically meaningful, have similar resource use (resource-homogeneous) and are important determinants of the total cost (2). For each of the analysed treatment processes, the frequency of activities (cost-drivers) should be established as well as unit cost of activities. The total cost can then be assessed by aggregating the product of the defined frequency and unit cost of each activity (1). Changes in the cost-drivers will cause changes in the total treatment cost, and thus focus on potential cost consequences of different treatment patterns. The ABC method has the potential to transform a hospital accounting system into a valuable management tool (1) by providing hospital and departmental management accurate cost information for treatment programs (2).

Technological innovations are significant drivers of rising costs in the healthcare sector and there has been an intense debate concerning the pros and cons of expensive robotic surgery, specifically given the increasing economic constraints within the healthcare system (3,4).

Increasingly, the current development within gynecological oncology is to make extensive use of surgical robots. Since 2005 when the Food and Drug Administration authorized the robotic-assisted approach in gynecology in the USA, the technique has spread rapidly in the developed world (5,6). Applications of robotic-assisted surgery are influenced by patient and surgeon's preferences and strong marketing (4,5). However, supplementary to the quality of patient outcomes, the cost of providing robotic-assisted surgery should also be taken into account. Purchasing and maintaining the robotic equipment, the potential for increased staff utilization and prolonged occupancy of the operating theater are all factors likely to impose substantially increased costs.

One gynecological application is to perform robotic-assisted laparoscopic hysterectomy (RALH) in patients with endometrial cancer. Total hysterectomy (HYS) and bilateral salpingo-oophorectomy (BSO) are indicated in patients with early stages of endometrial cancer and atypical complex hyperplasia (ACH), and in some cases surgical staging (7,8). Before the availability of RALH, patients with endometrial cancer were treated with total abdominal hysterectomy (TAH) by laparotomy. The traditional laparoscopic approach has not been widely used in gynecological oncology. Robotic-assisted surgery has now overcome some of the challenges of conventional laparoscopic surgery by offering surgeons a better range of motion, better three-dimensional visualization, and filtration of tremor during surgery (5,6,9,10).

The main disadvantage of robotic-assisted surgery is the high acquisition and maintenance cost. This cost is influenced by the monopoly market structure, with only one manufacturer marketing robotic surgical equipment (3,5,11). Therefore, RALH has increased the average treatment costs. It remains unclear to what extent the robotic procedure has improved patient outcomes, and whether the additional cost is justified by superior patient outcomes. However, the efficiency in resource utilization of the two operative procedures can be compared by analysing the difference in resource use and cost.

The hypothesis for this study was that for women with endometrial cancer or ACH, RALH is associated with shorter hospital stay (length of stay) and fewer complications than TAH, and that the longer occupancy of operating theater by the RALH procedure is balanced by a shorter observation period in the post-anesthetic care unit (PACU). Inclusion of these cost-drivers might change the cost differences between the two procedures. The aim was to conduct a cost analysis of treatment with RALH and TAH for women with endometrial cancer or ACH and to identify potential differences in resource use and cost between the operative modes.

Material and methods

From the outset, we decided to conduct the cost analysis solely from the perspective of the hospital and exclude resource use in the primary care sector and elsewhere. We also restricted the analysis to include resource use

Key Message

Robotic-assisted laparoscopic hysterectomy was cheaper than total abdominal hysterectomy for women with endometrial cancer due to shorter length of stay and less severe complications. Patients with increasing age and Type 2 diabetes seemed associated with higher costs.

associated with readmissions within 30 days after the initial operation, postoperative wound infections within 30 days, and severe postoperative complications within 4 months.

This study was conducted at the Department of Gynecology at Copenhagen University Hospital, Herlev, Denmark. The Department of Gynecology had access to one of the three robots at the hospital for 3½ work days weekly in the operating theater. Approximately 130 women are annually treated for endometrial cancer/ACH at the department. Four surgeons were trained to perform RALH, and five surgeons performed TAH. The department had an annual budget of 170 million Danish kroner (DKK) in 2015.

The RALH procedure applied a four-arm da Vinci S or da Vinci Si robot (da Vinci® Surgical System, Intuitive Surgical Inc., Sunnyvale, CA, USA) during general anesthesia. Pneumoperitoneum with carbon dioxide insufflation was established before the patient was positioned in steep Trendelenburg of 25–30°. The surgeon placed the robotic instrument trocars routinely for pelvic surgery and monopolar scissors; bipolar grasper, grasper and needle driver were used. No uterine manipulator was used. The vaginal cuff was closed using an absorbable Covidien™ 2-0 V-Loc continuous suture (Medtronic, Minneapolis, MN, USA). The TAH procedure was performed by laparotomy, transverse suprapubic or midline incision, using a self-retaining retractor and with the patient in about 15° Trendelenburg. Basic instruments for open surgery and a LigaSure™ vessel sealer (Medtronic) were used. The vaginal cuff was sutured continuously with an absorbable 2-0 suture.

For both surgical approaches, pelvic lymphadenectomy (PLA) was performed when more than 50% myometrial invasion (MI) was present or when indicated by high risk histology. Infracolic omentectomy (OM) was performed in the case of serous or clear cell carcinoma. All women received a single dose of prophylactic antibiotics at the beginning of surgery and low molecular heparin and antithrombotic stockings during the hospital stay. Staff observed the women postoperatively in the PACU as required.

We developed cost models for the two operative modes of hysterectomy [TAH (open) and RALH (robotic-assisted)] and for the two groups of patients (patients with HYS and BSO and patients with HYS, BSO and PLA and/or OM). During the model development, we identified different activities (cost-drivers) related to the "surgical process." These cost-drivers were clinically meaningful, resource-homogeneous and relevant to the overall cost of the operative procedure. The cost-drivers were: duration of surgery (operative time); duration of anesthesia; duration of stay in in the PACU; number of hospital bed days; occurrence of severe postoperative complications, specifically wound infections. For each of these cost-drivers we estimated unit costs based on data provided by the local Finance and Management Department.

Data on cost-drivers were obtained from journal and registry inspection. The study sample included two cohorts of women undergoing hysterectomy for endometrial cancer: all women treated with TAH from 1 March 2006 to 1 March 2009, and all women treated with RALH from 1 January 2013 to 1 September 2014. Individual data on operative time comprising duration of anesthesia and duration of PACU stay, were obtained from the Danish Anesthesia Database. The additional time spent on preparation for surgery and cleaning up after surgery was added to the duration of surgery (Table 1) after expert assessment. Data on number of hospital bed days (number of dates the patient was hospitalized), admission to Intensive Care Unit (ICU) (number of days the patient stayed in the ICU), and subsequent number of outpatient

Table 1. Resources of health care professionals needed in operating theatre during TAH and RALH

RALH and TAH	Preparation	Start of anaesthesia	Operative time	End of anaesthesia	Cleaning up
Senior Gynaecologist (2 Medical doctors)		+10 min for RALH/TAH			
Nurse Anaesthesiologist	+20 min. for RALH +15 min. for TAH				
Senior Anaesthesiologist MD					
Operating Theatre Nurse (2 Nurses)	+15 min. for RALH +7 min. for TAH				+10 min for RALH/TAH

This table shows additional time spent by the involved health care professionals for preparation or cleaning up. These additional minutes must be added on to the patient driven data of duration of operative time or time in anaesthesia

For example it is estimated that one of the two operating Theatre Nurses spend 15 minutes for preparation and 10 min for cleaning up. These minutes must be added to the mean anaesthesia time for RALH, similarly it took 7 minutes in preparation and 10 minutes post-surgery to assist for TAH.

Duration of operative time: Black, Duration of Anaesthesia: Light gray, Duration of work for Operating Theatre nurses: Dark gray

RALH: Robotic-assisted laparoscopic hysterectomy TAH: Total abdominal hysterectomy

visits related to the procedure as well as complications were obtained from the medical journal. Complications were defined as requiring surgical, endoscopic or radiological intervention or further treatment (≥3 on the Clavien–Dindo scale) (12) and wound infections as infections requiring revision in the operating theater.

Costs of instruments, disposables, waste, and service agreements with the robot manufacturer were identified and aggregated for an average patient for the TAH and RALH procedures. Additional costs for patients undergoing PLA and/or OM were added as average costs, estimated as the costs of additional disposables divided by number of patients undergoing PLA or OM. Costs associated with conversion to open surgery were not accounted for separately but was included in the duration of the operation accounted for in the time registration. The cost of maintaining the robot was assumed to be fully inclusive in the service agreement with the manufacturer. The service cost was based on the actual cost divided by an assumed annual number of procedures (300 per year). Two of three robots were funded by external sources, and the third robot was funded by the region/hospital. We consequently chose to exclude the purchase cost of the robots in our base case calculation but included the full cost in a sensitivity analysis. We assumed that one robot costs 16 million DKK, and converted the investment to annual equivalent cost assuming a 10-year lifetime, 4% discount rate and no scrap value. Surgeons, nurses, and industry contributed data for these costs.

The salary for a senior hospital physician (gynecology or anesthesia) was 900 000 DKK/year. Assuming an estimated 60% of working time (1628 clinical work hours per year) involving direct clinical patient contact, this amounts to an hourly wage of 921 DKK. We assumed the annual wage of the anesthetist (physician) to be 520 000 DKK. Again assuming that 60% of the working time was directly related to clinical patient contact, this amounted to an hourly wage of 532 DKK. The nurse anesthetists' annual wage was 460 000 DKK. Assuming 80% direct clinical patient contact, the hourly wage amounted to 353 DKK. Nurses in operating theater had an annual wage of 410 000. Assuming 80% direct clinical patient contact, the hourly wage amounted to 315 DKK. Similarly, for PACU nurses with a yearly wage of 440 000 DKK, the hourly wage amounted to 338 DKK.

The unit costs were provided by staff from the Hospital Financial Department. The price for one hospital bed day was 6507 DKK and for one ICU bed day 24 810 DKK. Additional outpatient visits were costed at 820 DKK (BG50A) from the Danish Diagnosis-Related Group (DRG) system (13).

The cost of complications after surgery (DRG 2102/DRG 2103) was set at 26 351 DKK, and 93 793 DKK in the case of a wound infection (DRG 1801) according to the Danish DRG system (13).

All prices are excluding taxes in DKK (2014 price level: 1€ = 7.5 DKK). Expenses for antibiotics, anesthesia, referral, pre-examination, diagnostics, and preparation for surgery and standard follow-up visits after surgery were similar in both groups and were therefore excluded from the cost analysis.

Statistical analysis

We reported continuous variables as means and standard deviations with 95% confidence intervals (CI). Discrete variables were reported as frequencies and percentages. We tested for outliers by visual inspection of scatterplots. Cost differences between groups were reported as absolute differences and percentages in relation to the cost of TAH. Cost data are often not normally distributed. Therefore the 95% confidence intervals are reported as bootstrap intervals ($n = 1000$). Sensitivity analyses assessed the effect of including costs of investment in the robot and excluding costs related to complications. We analysed the variation in cost data by ordinary least-squares regression with all baseline characteristics included in a full model and with only significant variables included in a reduced model. All p-values are reported as two sided. A p-value <0.05 was considered statistically significant. Data were analysed using SPSS version 19.9 (SPSS Inc. Chicago, IL, USA) and with Microsoft EXCEL 2010 (Microsoft Corp., Redmond, WA, USA).

The study was reported according to Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guidelines (14). Danish Health and Medicines Authority (3-2013-111/1/KAHO) and the Head of Department of Gynecology, Copenhagen University Hospital, Herlev, approved the acquisition of data from patient records. Data collection was approved by the Danish Data Protection Agency (2207-58-015/HEH.750.16-27).

Results

The cost analysis was based on data from 158 women treated with TAH and 202 women treated with RALH. The pre-operative characteristics of the two cohorts are reported in Table 2. The groups were similar at baseline with the exception that more women consumed >7 units of alcohol per week in the RALH group.

The costs of consumables for the two procedures are summarized in Table 3. The TAH procedure required consumables equivalent to 3830 DKK per procedure. The RALH required consumables equivalent to 16 472 DKK,

Table 2. Pre-operative characteristics (n = 360).

	TAH HYS+BSO (n = 85)	RALH HYS+BSO (n = 153)		TAH HYS+BSO+PLA/OM (n = 73)	RALH HYS+BSO+PLA/OM (n = 49)	
	Mean [SD]/n (%)		p-values	Mean [SD]/n (%)		p-values
Age (years)	69 [11.8]	67 [11.7]	0.34[c]	68 [9.6]	71 [9.8]	0.21[c]
Body mass index						
Obese ≥30	33 (39)	64 (42)	0.68[d]	18 (25)	11 (22)	0.83[d]
Smoker	12 (14)	17 (11)	0.55[d]	8 (11)	6 (12)	1.0[d]
Alcohol consumption						
More than 7 units/week	10 (12)	37 (24)	0.04[d]	7 (10)	12 (25)	0.04[d]
ASA-score						
I+II	74 (87)	122 (80)	0.07[d]	64 (88)	45 (92)	0.76[d]
Cardiovascular disease[a]	41 (48)	78 (51)	0.79[d]	37 (51)	21 (43)	0.46[d]
Respiratory disease[b]	5 (6)	12 (8)	0.79[d]	2 (3)	3 (6)	0.39[d]
Diabetes type II	10 (12)	16 (11)	0.83[d]	10 (14)	5 (10)	0.78[d]

ASA, American Society of Anesthesiologists; BSO, bilateral salpingo-oophorectomy; HYS, hysterectomy; OM, omentectomy; PLA, pelvic lymphadenectomy; RALH, robotic-assisted laparoscopic hysterectomy; TAH, total abdominal hysterectomy.

[a]Cardiovascular disease definition: hypertension, atrial fibrillation, arteriosclerotic heart disease, heart failure. New York Heart Association Classification of Heart Failure: 1 – Cardiac disease, but no symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, climbing stairs. 2 – Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.

[b]Respiratory disease definition: chronic obstructive pulmonary disease, asthma, emphysema.

[c]Independent sample t-test.

[d]Fisher's exact test.

excluding the cost of robot investment; the amount was 21 805 DKK when including this cost. The average cost of consumables for TAH was 12 642 DKK less than for RALH. The distribution of cost-drivers is shown in Table 4. There were a few outliers: operative time >250 min (n = 4); duration of anesthesia >450 min (n = 2); duration of stay in PACU >850 min (n = 2). However, excluding these outliers did not cause an important change in the estimated mean difference or p-values. Therefore all outliers were retained in the analysis.

The distribution of the average cost by different cost-drivers is illustrated in Figure 1. For women with HYS+BSO we estimated the mean total costs for the TAH cohort as 55 223 DKK and for the RALH cohort 44 653 DKK. The difference of 10 570 DKK (Table 5) (corresponding to 19% lower cost for RALH) was statistically significant (p = 0.02). For women with HYS+BSO+PLA/OM the mean total cost was 55 780 DKK for TAH and 52 190 DKK for RALH. The difference of 3590 DKK (6% lower cost for RALH) was not statistically significant (p = 0.40). Overall, the RALH procedure was 9386 DKK cheaper (17%) than the TAH procedure (p = 0.003): 55 555 [95% CI (bootstrap) 51 198, 60 848] vs. 46 169 [95% CI (bootstrap): 44 110, 48 480]. When stratifying the cost analysis to the TAH cohort, the cost difference of women with HYS+BSO and women with HYS+BSO+PLA/OM was 557 DKK (p = 0.90) mainly due to longer surgical time. In the robotic cohort the cost difference was 7537 DKK (p = 0.02) due to longer surgery. In the analysis where the cost of the robot investment was included, the cost difference between the TAH and RALH cohorts amounted to 4053 DKK (RALH 7% cheaper than TAH; p = 0.2): 55 555 [95% CI (bootstrap): 50 939, 60 486] vs. 51 502 [95% CI (bootstrap): 49 418, 53 839). In the analysis where the cost of complications was excluded, the cost difference amounted to 6054 DKK (RALH 12% cheaper than TAH; p = 0.02): 51 106 [95% CI (bootstrap): 47 698, 55 553] vs. 45 052 [95% CI (bootstrap): 43 599, 46 850].

In the regression analysis (Table 6) the reduced model showed that RALH was 9119 DKK cheaper than TAH. The regression model showed that for every year of higher age, the cost of the hysterectomy procedure increased by about 500 DKK. Type 2 diabetes increased overall costs by about 11 700 DKK.

Discussion

This cost analysis confirmed the hypothesis that for women with endometrial cancer or ACH the RALH procedure is cheaper than the TAH procedure. The lower cost is mostly due to fewer complications and shorter length of hospital stay after the procedure. In the base case analysis we excluded cost related to the robot investment. However, when including the cost of the robot, the RALH procedure was no longer statistically significantly

Table 3. Cost of consumables during operative procedures (2014 DKK).

Type of surgery	TAH per surgery		RALH per surgery	
Instruments	Basic instruments – 1	143	Cameraport	400
	Basic instruments – 2	166	Robot port (3 × 14)	42
	Magnetic mat	61	Monopolar scissors	2400
	Surgical handle	25	Bipolar grasper	2025
			Grasper	1650
			Needle driver	1650
			Airport seal	1400
Disposables	LigaSure™	2500	Da Vinci draping (disposable accessory kit 4 arm)	1755
	Catheter and washing	25	Draping	817
	3M Procedure kit	381	Catheter and washing	25
Material for suturing	Sutures	300	Sutures	125
Waste	2 sacks	30	3 sacks	45
Service agreement with robot manufacturer 1.2 million DKK/year/300 surgeries	–		4000	
Total costs for HYS+BSO	3631		16 334	
Additional cost for PLA/OM[a]	199		138	
Total cost	3830		16 472	
Robot cost (daVinci SI) 16 million DKK Amortization over 10 years 300 procedures/year	–		5333	
Total costs including robot cost	–		21 805	

Prices without taxes in DKK. All data has been collected from clinical staff, the Hospital Financial Department and the manufacturers.
BSO, bilateral salpingo-oophorectomy; DDK, Danish kroner; HYS, hysterectomy; OM, omentectomy; PLA, pelvic lymphadenectomy; RALH, robotic-assisted laparoscopic hysterectomy; TAH, total abdominal hysterectomy
[a]Weighted cost for pelvic lymphadenectomy and omentectomy.

cheaper. Two of the three robots at our center are externally funded and the cost of the third robot has been financed by the region. In health economic evaluations of robotics it is debatable whether the robot investment should be included or not (15,16). Those who support including the cost, argue that the investment is significant and should be included, whereas opponents argue that the robot often is funded externally and a one-time investment, and is therefore not a direct cost for the hospital. Here, we analysed both situations and both showed that RALH was cheaper than TAH, although when the investment cost was included, the cost difference was statistically insignificant.

Complications were important for the total cost and when these costs were excluded, the cost difference between the two operative procedures was still significant. We adopted a conservative approach towards categorizing complications, only including severe complications (complications grade ≥3 measured on the Clavien Dindo scale). It is possible that this may have reduced the impact of complications on cost. Several previous studies have concluded that RALH is more costly than TAH when the cost perspective is restricted to the cost of surgery alone (6,15,17). This concurs with our findings concerning specifically surgery cost, which in our study was more than four times higher for RALH. However, including patient outcomes in the calculation changes the overall conclusion and makes RALH a favorable alternative to TAH, in line with results of others (18). In the Society of Gynecologic Oncology consensus statement it is recommended that cost analyses include direct and indirect costs and preferably both operating theater supplies, equipment, operating and PACU time, physicians' salaries, hospital room and board and laboratory, radiology, and pharmacy costs (19). We have complied with these recommendations except for the latter three cost components, as we considered laboratory, radiology, and pharmacy costs to be equal in both groups. Furthermore, the consensus statement suggested accounting for costs due to complications, caregiving, and lost productivity associated with recovery (19). The two last issues were not covered in our study.

Over the years, hospital managers have focused on ways to reduce the length of hospital stay as a way to improve efficiency. This may in part explain some of the difference in the length of hospital stay for the two cohorts. For TAH, the length of hospital stay was the driving force behind the increased costs in this study,

Table 4. Cost-drivers: real resource usage for hysterectomy procedures.

Activity	Unit	"Cost-driver" used in model			
		TAH (HYS +BSO) (*n* = 85)	TAH (HYS+ BSO+ PLA/OM) (*n* = 73)	RALH (HYS+BSO) (*n* = 153)	RALH (HYS+ BSO+ PLA/OM) (*n* = 49)
Operative time	Time spent min. Mean (SD)	91 (30)	114 (34)	104 (28)	173 (50)
	95% CI	[84.6; 97.5]	[106.2; 121.8]	[99.6; 108.4]	[159;187]
Anesthesia time	Time spent min. Mean (SD)	172 (73)	190 (45)	201 (36)	284 (106)
	95% CI	[156.5; 187.5]	[179.7; 200.3]	[195.3; 206.7]	[254.3; 313.7]
Time in PACU	Time spent min. Mean (SD)	456 (230)	455 (211)	181 (81)	201 (195)
	95% CI	[407.1; 504.9]	[406.6; 503.4]	[168.2; 163.8]	[146.4; 255.6]
LOS	Time spent days. Mean (SD)	6.1 (4.1)	5.9 (2.6)	3.0 (1.7)	3.3 (2.1)
	95% CI	[5.2; 7.0]	[5.3; 6.5]	[2.7; 3.3]	[2.7; 3.9]
ICU	Time spent days/*n*	2 (*n* = 1)	0	0	0
Additional ambulatory visits	Number of visits, SUM	–	–	28	8
Complications requiring subsequent surgical, endoscopic or radiological intervention or more (>3 on the Clavien–Dindo scale) (excluding wound infection)	Number of cases *n* (%)	9 (11)	7 (10)	4 (3)	1 (2)
Wound infection requiring revision in operating theater	Number of cases *n* (%)	1 (1)	2 (3)	–	1 (2)

All clinical data were collected from hospital records.
BSO, bilateral salpingo-oophorectomy; HYS, hysterectomy; ICU, intensive care unit; OM, omentectomy; PLA, pelvic lymphadenectomy; RALH, robotic-assisted laparoscopic hysterectomy; LOS, length of stay; PACU, post anesthetic care unit; TAH, total abdominal hysterectomy.

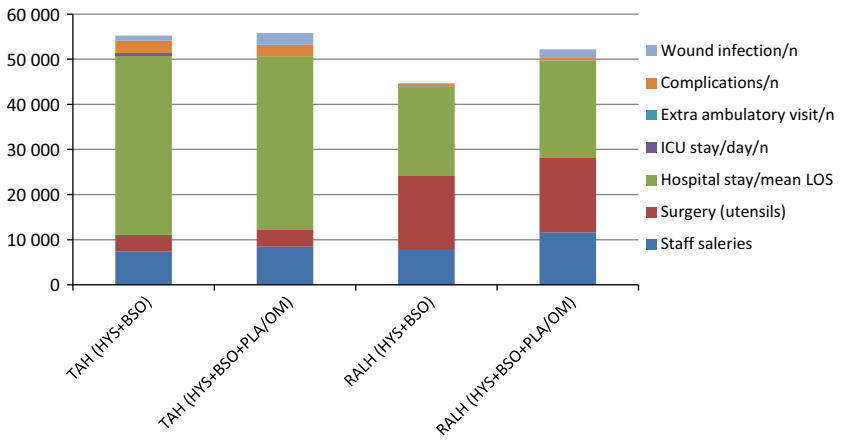

Figure 1. Distribution of mean costs of the two types of surgery and the two patient groups.
Visual supplement of data presented in table 4. TAH, total abdominal hysterectomy; HYS, hysterectomy; BSO, bilateral salpingo-oophorectomy; PLA, pelvine lymphadenectomy; OM, omentectomy; RALH, robotic-assisted laparoscopic hysterectomy; ICU, intensive care unit; LOS, length of stay.

similar to other studies (18,20). We considered using the diagnosis-related groups (DRG) as the measure of costs, but refrained from doing so as DRGs would be different for the two cohorts because they represent two different time periods. Furthermore, the DRG codes may change annually and the coding practice may also differ from year to year. We found it most valid to report severe complications as they were recorded clinically in the patient journal and price them using the 2014 DRG tariffs.

Drinking more than 7 units of alcohol per week was unevenly distributed pre-operatively between the groups. We therefore addressed this in the least ordinary squared regression but were unable to identify a significant impact

Table 5. Distribution of mean cost of the two types of surgery and the two patient groups.

	TAH		RALH	
	HYS+BSO (n = 85) Mean (SD)	HYS+BSO+PLA/OM (n = 73) Mean (SD)	HYS+BSO (n = 153) Mean (SD)	HYS+BSO+PLA/OM (n = 45) Mean (SD)
Salaries	7423 (NA)	8462 (NA)	7959 (NA)	11 659 (NA)
Surgical utensils	3631 (NA)	3830 (NA)	16 334 (NA)	16 472 (NA)
Hospital stay	39 692 (26 660)	38 391 (17 001)	19 521 (10 785)*	21 473 (13 789)*
ICU stay	584 (5382)	0	0	0
Extra ambulatory visit	0	0	150 (583)*	134 (454)
Treatment for complications	2790 (8155)	2527 (7813)	689 (4218)*	538 (3764)
Treatment for wound complications	1103 (10 173)	2570 (15 417)	0	1914 (13 399)
Overall cost per patient	55 223 (36 605)	55 780 (24 799)	44 653 (12 664)*	52 190 (21 591)
Overall cost	55 555 (31 608)		46 169 (15 601)*	
Overall cost including robot investment	55 555 (31 608)		51 502 (15 601)	
Overall cost excluding cost for complications	51 106 (25 522)		45 052 (11 850)*	

NA – cost estimated deterministically and therefore no SD can be calculated.
BSO, bilateral salpingo-oophorectomy; HYS, hysterectomy; ICU, Intensive care unit; OM, omentectomy; PLA, pelvic lymphadenectomy; RALH, robotic-assisted laparoscopic hysterectomy; TAH, total abdominal hysterectomy.
*$p < 0.05$ between TAH and RALH within same patient group determined by independent-sample t-test with $n = 1000$ bootstrap value.

Table 6. Ordinary least-squares regression.

	Full model		Reduced model	
	B	t	B	t
RALH	−10 211	−3.804**	−9119	−3.647**
Age	440	3.368**	514	4.483**
BMI >30	78	0.028	–	
Cardiovascular disease	1380	0.501	–	
Pulmonary disease	7573	1.352	–	
Type 2 diabetes	11 247	2.674**	11 721	2.928*
ASA score >2	1523	0.782	–	
Smoker	−7917	−2.027*	−7432	−1.958
Alcohol >7 units/week	−2844	−0.869		–
Endometrial cancer	−5109	−1.275	–	
Constant	17 422	1.414	17 460	1.728
R^2	0.38		0.36	

ASA, American Society of Anesthesiologists – classification of physical health score; BMI, body mass index; RALH, robotic assisted laparoscopic hysterectomy.
*$p < 0.05$; **$p < 0.01$.

on overall costs. The regression model confirmed that RALH was less costly than TAH, and that Type 2 diabetes and increasing age are associated with higher costs. A previous study found that women older than 80 years developed significantly more grade III and IV complications compared with younger women (21), which could explain the increased cost. The underlying pathologies in Type 2 diabetes can perhaps explain the associated higher cost. Uncontrolled blood glucose can lead to microvascular complications and increases the risk of macrovascular complications (22), which may be linked to longer length of stay.

Our results indicated that body mass index (BMI) >30 was not associated with increased cost. A previous study found that high BMI was not associated with an increased frequency of complications until it exceeded 50 (23). Another study found that total laparoscopic hysterectomy for obese patients with a BMI >35 was not cost-effective because of the high conversion rate (32%) (24). However, in comparison, only 2% of women in our RALH sample were converted to open surgery.

It is to be expected that expanded surgery will be more costly, as we found in surgery including PLA/OM regardless of operative mode. However, the difference was less in the TAH group. The prolonged operative time and higher cost may be the reason why surgery is more expensive with PLA/OM. Furthermore, for both surgical modes, cost linked to wound complications was higher for women having PLA/OM. This concurs with findings of a large study of women with endometrial cancer which showed that surgical site infections increased costs. In addition, PLA and longer operative time were associated with organ/space surgical site infection (25).

An important strength of this cost study is the application of detailed data on important cost-drivers. Such data provide more accurate costs and give insights into the cost structure (2). Furthermore, it is a strength that the study builds on real-life data from a large group of women (n = 360) who had a hysterectomy, rather than on theoretical assumptions and expert guesses. The validity of the operating theater time (operative time) is

emphasized by the fact that the data did not include any learning cases, as RALH had been performed routinely for 4 years before these data were recorded. A limitation is the lack of societal data as requested by the Society of Gynecologic Oncology consensus statement (19). Regrettably, we did not have access to patient data after hospital discharge. An inherent limitation is the use of retrospective data from patient records and the time gap between the two cohorts used in this study.

To conclude, this cost analysis showed that RALH is cheaper than TAH. From an overall point of view, RALH provided better health outcomes for women with shorter length of stay and less severe complications. This counterbalanced the high cost for the actual robotic surgery. It would be beneficial for further research to focus on time spent returning to normal activity and levels of health-related quality of life after RALH. Patient-reported outcomes are warranted in creating the full picture of potential benefits and harms of this relatively new treatment – robotic-assisted laparoscopic hysterectomy.

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Health-related quality of life after robotic-assisted laparoscopic hysterectomy for women with endometrial cancer — A prospective cohort study

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HIGHLIGHTS

- RALH does not have a prolonged negative effect on general health.
- Ability to perform work or hobbies was still negatively affected at 5 weeks.
- Fatigue, pain and gastrointestinal symptoms were negatively affected short term.

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ABSTRACT

Objective. The aim of this prospective cohort study using patient-reported outcome measures (PROMs) was to detect short term changes in functioning, symptoms and health-related quality of life (HRQoL) after robotic-assisted laparoscopic hysterectomy (RALH) for endometrial cancer or atypical complex hyperplasia.

Methods/materials. A total of 139 women answered the EORTC C-30, EN-24 and EQ-5D-3L preoperatively (baseline) by face to face interview and again 1 week, 5 weeks and 4 months postoperatively by telephone interview. The women furthermore reported their level of activity compared to their habitual level in a diary during the first 5 weeks after surgery.

Results. We found a clinically relevant decrease in HRQoL after 1 week. At 5 weeks postoperatively, HRQoL was again at the preoperative level. Fatigue, pain, constipation, gastrointestinal symptoms, and appetite were all negatively affected 1 week postoperatively, but back to baseline level at 5 weeks. Ability to perform work or hobbies and change of taste were still affected at 5 weeks.

Conclusions. HRQoL and postoperative symptoms were overall back to the preoperative level 5 weeks after RALH. These findings indicate fatigue, pain, constipation, gastrointestinal symptoms, appetite, ability to perform work and hobbies, change of taste and sexually related problems should be addressed in future research and in the pre- and postoperative care for women undergoing RALH.

1. Introduction

Patient-reported outcome measures (PROMs) are increasingly recognized as important for evaluation of treatment effectiveness and patient progress [1–4]. PROMS provide insight into patients' perspectives on health, symptoms and care without the interpretation of a clinician or anyone else [5]. PROMs should include an assessment of symptoms, function (physical, sexual or emotional) as well as health-related quality of life (HRQoL) [6]. PROMs are relevant and in demand in clinical practice [1], in cancer research in general [7] and in research concerning women with endometrial cancer [3,8].

Endometrial cancer is the most common cancer in the female genital tract in the developed world and the incidence is rising due to sedentary lifestyle and obesity in high income countries [3]. Annually, 750 women are diagnosed with endometrial cancer in Denmark [9]. Endometrial cancer has the highest incidence in women between 60 and 69 years of age. These women often have multiple medical comorbidities such

Abbreviations: ACH, atypical complex hyperplasia; ASA, American Society of Anesthesiologists physical status classification system; BMI, body mass index; CVD, cardiovascular disease; EORTC, European Organisation for Research and Treatment of Cancer; GHS, general health score; HRQoL, health-related quality of life; LOS, length of stay; PROMs, patient-reported outcome measures; QoL, quality of life; RALH, robotic-assisted laparoscopic hysterectomy; SD, standard deviation.

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as diabetes, cardiovascular disease (CVD) and obesity [10]. The five-year survival rate is 80% for all stages of endometrial cancer [10].

Hysterectomy and bilateral salpingo-oophorectomy is the basic treatment of endometrial cancer [10]. Since 2005 it has been possible to perform hysterectomy by robotic-assisted laparoscopy (RALH) and throughout the last decade this treatment option has spread rapidly in high income countries. Diminished surgical trauma facilitates rapid recovery after RALH. There is, however, scarce evidence both concerning HRQoL immediately after RALH and the time needed to regain habitual level of activity postoperatively [3]. In general, we have minimal knowledge of HRQoL in women with endometrial cancer [3,8]. Studies have previously focused on postoperative complications [11], length of surgery [12], blood loss [11,13], learning curves for surgeons [14], length of stay (LOS) [11] and costs [15]. Following surgery for endometrial cancer, gastrointestinal, urinary, and sexual functions are potentially affected, perhaps especially in elderly women with comorbidities [3]. Knowledge of the recovery period is important to clinicians to tailor preventions, information and follow-up adequately.

The primary aim of the study was to prospectively examine HRQoL, symptoms and functional level in the immediate postoperative period defined as the first 4 months after surgery. Secondly, the aim was to examine potential associations between socio demographic variables and HRQoL over time in women treated by RALH for endometrial cancer or atypical complex hyperplasia (ACH).

2. Material and methods

2.1. Study population

We included 139 women treated with RALH (total hysterectomy) for endometrial cancer or ACH from January 1. 2013 to September 1. 2014 at Copenhagen (University Hospital, Herlev). Exclusion criteria were: radical hysterectomy, adjuvant treatment (chemotherapy or radiation), non-proficient in Danish, not cognitively able to fill in questionnaires and impaired hearing (not able to answer questions per telephone).

2.2. Outcomes

The primary outcome was HRQoL measured by the European Organization for Research and Treatment of Cancer (EORTC) QLQ C-30 (cancer specific) and EN-24 (endometrial cancer specific) [16]. Secondary outcomes were HRQoL measured by Euroqol-5D (EQ-5D-3L) [17], self-rated health (5 levels) [18], and postoperative level of activity as a percentage of the patients' habitual level of activity.

2.3. Tools and single item questions

To assess generic HRQoL we used EQ-5D-3L [17] in the Danish translation. This is a standardised, generic instrument developed to describe and rate health [19] and it is increasingly used in gynaecology [20,21]. Each of the five domains comprising the EQ-5D-3L is assessed by a single question with three levels of response describing the severity of a patient's problems in the domain. The domains are mobility, self-care, usual activities, pain/discomfort and anxiety/depression. In addition, participants were asked to rate their general health on a visual analogue scale (EQ-5D-VAS) from 1 to 100, with 1 representing the worst state and 100 representing the best imaginable state. To assess illness-specific HRQoL, we used the EORTC QLQ C-30 and EN-24 [16] originally developed for cancer patients, and the EN-24 specifically for endometrial cancer. Participants were asked to rate their physical, psychological and social well-being in the preceding week. Together, the two questionnaires contained 54 items, the majority of which were rated on a scale from 1 to 4 where 1 "is not at all" and 4 is "very much". The EORTC QLQ C-30 and EN-24 are validated [22] and translated into Danish. Raw scores were converted to a 0–100 scale according to the scoring manual of the EORTC Quality of Life Group [23]. Missing values were handled as suggested in the manual [23], i.e. if sub-scales had less than half of the items missing, the mean value of the sub scale was imputed and no single item measures were imputed. Higher scores on the QLQ C-30 functioning and the global quality of life (QoL) scale indicated better functioning or QoL, whereas higher scores on the symptom scales represented a higher level of symptoms. A higher score on items related to sexuality (sexual interest, sexual activity and sexual enjoyment) in the QLQ EN-24 module indicated better sexual functioning. Questions (51–54) related to sexuality presume sexual activity and were therefore optional. For these items only scores from sexually active women were computed. Questions concerning sexuality (Questions 49–54) were only included at baseline (the last week day before surgery) and at 4 months as the women were advised to abstain from intercourse for the first 6–8 weeks after surgery.

The women were furthermore asked at baseline and 4 months postoperatively to rate their level of health with the single item question: "In general, how would you rate your health today?" with the options "Very bad", "Bad", "Moderate", "Good" or "Very good" [18]. Finally, during the first 5 postoperative weeks, the women were asked to assess their level of daily activity compared to their habitual preoperative level once a week in a diary.

2.4. Procedure for data collection

Two research assistants (instructed by the first author) approached eligible women in the hospital in connection with the planning of surgery. They informed eligible patients orally and in writing about the study. The first author or the research assistants obtained informed consent to participate from the women who wished to do so. Baseline variables and patient demographics were collected face to face on the last weekday before surgery. The first author or the research assistants collected follow-up data on participants' HRQoL at 1 week, 5 weeks and 4 months after RALH by telephone interviews.

2.5. Data analysis and statistics

Double data entry was done and we compared the two datasets for any discrepancies. Potential differences between included women and those not included/excluded were explored.

Mean scores and standard deviations (SD) were calculated for the multi-item and single-item scales.

Changes in HRQoL in the EORTC C-30 and EN −24 within 4 months postoperatively were examined using a Linear Mixed Model analysis. This analysis is relevant when analysing unbalanced data with repeated measures (correlated data) [24]. We considered differences in EORTC scale scores of 10 points or more clinically relevant [25].

EQ-5D-3L scores were reported as a binary outcome – stating no problem or problems in each of the 5 domains and reported as numbers and percentages of the sample. A 10% change in distribution was considered clinically relevant [26]. EQ-VAS scores were reported as means with SDs and mean differences from baseline and were analysed by Linear Mixed Model Analysis. Differences in the EQ-5D-VAS scores over time were tested for subgroups of women. The subgroups were: age > 70 years, BMI > 40, pelvic lymphadenectomy performed, ASA score 3, single women, women with <9 years of school and women with >4 years of education. The test was an analysis of the interaction between subgroups and time points of measurement.

Self-rated health was analysed using the non-parametric Wilcoxon Signed Rank test for differences. For differences between levels of activity we used Linear Mixed Model analysis. All calculated p values were two sided and we considered $p < 0.05$ statistically significant. Data was analysed using SPSS version 19. 9 (Inc., Chicago, Il, USA).

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2.6. Ethics

Participants gave oral and written consent to participate. The Danish Data Protection Agency gave permission to store trial data (2007–58-0015/HEH.750.16–27). The National Committee on Health Research Ethics assessed the study and did not deem further formal approval necessary (H-2-2012-FSP26). The study was reported to ClinicalTrials.gov (NCT01761721).

3. Results

In this study we screened 202 women, 49 women were not included (reasons being schizophrenia (n = 1), dementia (n = 5), not Danish speaking (n = 6), non-hearing (n = 1), lost to logistics (n = 7) and declining participation (n = 29)) leaving 153 to be included. During the study, 14 women were excluded (need for chemotherapy (n = 10) or withdrawal of consent (n = 4)). The study population consisted of 139 women treated by RALH, of which 135 completed follow-up at all four time points of measurements. In total, 114 completed and returned the patient diary. The double data entry showed a discrepancy of 2% between the two datasets, which was corrected prior to data analysis. Analysis of differences between included and not included/excluded women showed that included women had significantly less comorbidity (fewer women with CVD and with ASA 3) and also a significantly higher BMI. Socio-demographic and clinical characteristics are shown in Table 1.

Scores on the EORTC QLQ C-30 (Table 2) indicated a significant decline in role function (performing work or hobbies) from baseline to 1 week and a significant rise from 1 week to 5 weeks with the score returning to baseline level at 4 months. The general health score (GHS) increased significantly from 1 to 5 weeks. The women experienced significantly increased fatigue, pain, loss of appetite, constipation, and gastrointestinal symptoms (faecal incontinence, flatulence, bloating, stomach cramps) from baseline to 1 week but all symptoms were close to baseline values by 5 weeks. There was a significant increase in change of taste from baseline to 1 week. These symptoms were resolved at 4 months (Table 2). Analyses of the level of sexual interest and the level of sexual activity were done in a reduced sample. We found reduced sexual interest and activity at 4 months compared to baseline (not clinically relevant but statistically significant p = 0.002 and p = 0.001). Sexual or vaginal problems had increased at 4 months for sexually active women (not clinically relevant but statistically significant p = 0.04).

A clinically relevant improvement in general health assessed by EQ-5D-3L and in mobility was seen from 1 to 5 weeks. After 1 week, there was a clinically relevant decline in the ability to carry out usual activities, however, this had improved at 5 weeks and was back to baseline level at 4 months. Forty-three percent reported problems with pain/discomfort at 1 week declining to 19% at 5 weeks. At 5 weeks, problems with pain/discomfort affected fewer women compared to baseline. Similarly, there was a decline in the number of women experiencing anxiety/depression, 35% at baseline and 21% 1 week after surgery. The percentage of women experiencing anxiety/depression remained unchanged at the subsequent measuring points. When rating general health on a score from 1 to 100 there was a decline at 1 week; however the general health score increased significantly at all of the following time points (p = 0.001)(Table 3).

Differences in the EQ-5D-VAS over time were tested for subgroups (age > 70 years, BMI > 40, pelvic lymphadenectomy performed, ASA score 3, single women, women with <9 years of school and women with >4 years of education) and interaction with time. This analysis showed that women with >9 years of school rated their general health similar to women with less schooling over the first time points. However, women with >9 years of school rated their general health significantly higher at 4 months (p value 0.003). Women with ASA score 3 rated their general health lower in comparison to women with ASA 1 or 2 at all-time points (p value = 0.03). All other subgroup analyses of interactions were non-significant.

Compared to the preoperative rating, self-rated level of health improved for 48 (35%) women and deteriorated for 21 (15%) within 4 months postoperatively (p = 0.001)(Fig. 1).

In the patient diary, the women were asked to rate the percentage of habitual daily activity they were able to perform, presupposing 100% as their habitual preoperative level of daily activity. At the end of 1 week, the mean level of activity was 56% (SD: 24.5), at 2 weeks the mean level was at 73% (SD: 22.0), at 3 weeks it was 77% (SD: 20.4), at 4 weeks it was 83% (SD: 18.7) and, finally, at 5 weeks the mean level of activity was 84% (SD: 18.7) (p value <0.001) (Fig. 2). However, at 5 weeks, several women reported that they were reluctant to assess their level of activity level to be 100% as they had not yet resumed strenuous activities such as horseback riding, sea-bathing or fitness.

Table 1
Socio-demographic and clinical characteristics at baseline n = 139.

	Mean (SD) (range)	n (%)
Age (years) 41–50		11 (8)
51–60		32 (23)
61–70		39 (28)
71–80		42 (30)
81–90		15 (11)
BMI	29 (7.3) (18–51)	
Obese class III > 40		14 (10)
Cardiovascular disease[a]		58 (42)
Pulmonary disease[b]		11 (8)
Type 2 diabetes		15 (11)
Smoker		16 (12)
Alcohol consumption > 7 units/week		30 (22)
ASA-score		
I. + II		122(88)
III.		17 (12)
Civil status		
Single		63(55)
Cohabitating/married		76 (45)
School		
Completed less than 9 years of school		40 (29)
Completed more than 10		99 (71)
Education level		
None/<4 years of education		122 (88)
Completed education longer than 4 years		17 (12)
Type of surgery		
HYS + BSO		109 (78)
HYS + BSO + PLA AND/OR OM		30 (22)

ASA-score: American Society of Anaesthesiologists.
HYS: hysterectomy. BSO: bilateral salpingo-oophorectomy. PLA: pelvic lymphadenectomy. OM: Omentectomy.
[a] Hypertension, atrial fibrillation, arteriosclerotic heart disease, heart failure. New York Heart Association Classification of Heart Failure 1 — cardiac disease, but no symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, and climbing stairs. 2. Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
[b] Chronic obstructive pulmonary disease, asthma, emphysema.

4. Discussion

We found that HRQoL was negatively affected 1 week after surgery but back to preoperative baseline levels within 5 weeks. A randomized clinical trial of women undergoing laparoscopic or laparotomy for endometrial cancer reported similar findings [27]. Kornblith and colleagues assessed HRQoL using the FACT-G questionnaire. They found that in the laparoscopy group, HRQoL was above baseline level after 6 weeks, while the laparotomy group first reached their baseline level at 6 weeks [27]. Unfortunately they did not have a 5 week measuring point.

In the present study, the women reported decreased ability to perform work (in the workforce or domestic work) and hobbies (Role

Table 2
EORTC QLQ C-30 and EN-24 mean scores from baseline to 4 months after RALH.

	Baseline mean [SD]	1 week	5 weeks	4 months	p value for the full model
EORTC QLQ C-30					
Functional scales					
Physical	84.6 [19.4]	72.6 [22.3][c]	81.3 [21.3]	86.0 [19.9]	<0.001[a]
n	139	133	135	135	
Role	81.5 [28.1]	44.8 [33.4][c]	77.1 [29.5][c]	88.0 [25.5][c]	<0.001[a]
n	139	132	134	135	
Emotional	73.7 [20.2]	83.3 [21.5]	88.3 [18.1]	86.9 [21.3]	<0.001[a]
n	139	135	135	135	
Cognitive	86.5 [19.8]	87.3 [20.3]	90.6 [19.1]	90.2 [18.4]	0.08[a]
n	139	135	135	135	
Social	94.1[17.0]	90.8 [19.6]	94.2 [17.3]	95.3 [15.6]	0.01[a]
n	139	134	135	135	
GHS	71.1 [22.3]	65.9 [22.1]	80.5 [19.0][c]	83.0 [20.5]	0.001[a]
n	139	134	135	135	
Symptom scales					
Fatigue	22.3 [22.3]	46.1 [26.5][c]	23.9 [25.1][c]	18.6 [25.2]	<0.001[a]
n	139	135	135	135	
Nausea and vomiting	3.5 [10.3]	9.5 [18.8]	2.5 [10.7]	3.0 [10.7]	0.001[a]
n	139	135	135	135	
Pain	16.1 [21.5]	29.6 [26.4][c]	12.3 [22.7][c]	11.9 [22.6]	<0.001[a]
n	139	135	135	135	
Dyspnoea	9.8 [22.2]	14.3 [27.1]	7.7 [19.1]	6.7 [18.1]	0.03[a]
n	139	135	135	135	
Insomnia	31.2 [33.1]	24.6 [32.2]	20.5 [29.9]	22.7 [33.0]	0.01[a]
n	139	134	135	135	
Loss of appetite	9.1 [23.7]	23.5 [32.3][c]	8.0 [22.1][c]	6.2 [21.6]	<0.001[a]
n	139	135	134	135	
Constipation	5.0 [17.0]	16.7 [29.0][c]	5.4 [14.2][c]	4.4 [15.7]	<0.001[a]
n	139	135	135	135	
Diarrhoea	7.2 [18.7]	14.3 [25.0]	4.2 [15.5][c]	4.4 [14.0]	<0.001[a]
n	139	135	135	135	
Financial difficulties	2.8 [16.8]	3.3 [17.3]	3.5 [16.6]	2.7 [14.7]	0.8[a]
n	138	133	133	135	
EORTC QLQ EN-24					
Functional scales					
Sexual interest	86.0 [23.6]	–	–	79.4 [25.6]	0.002[b]
n	137	–	–	128	
Sexual activity	88.8 [21.8]	–	–	82.3 [23.6]	0.001[b]
n	139	–	–	128	
Sexual enjoyment[d]	18.9 [25.8]	–	–	39.1 [32.4][c]	0.08[b]
n	30	–	–	46	
Symptom scales					
Lymphoedema	8.4 [17.2]	6.5 [16.4]	7.0 [17.2]	15.3 [25.7]	<0.001[a]
n	139	135	135	135	
Urological symptoms	13.1 [16.0]	12.9 [16.7]	10.4 [15.0]	11.7 [16.7]	0.03[a]
n	139	132	134	134	
Gastrointestinal sympt.	8.4 [12.3]	22.2 [17.0][c]	9.1 [14.6][c]	9.5 [14.7]	<0.001[a]
n	139	135	135	135	
Poor body image	5.1 [14.4]	11.3 [21.5]	3.3 [12.6]	2.1 [10.5]	<0.001[a]
n	137	133	132	133	
Sexual/vaginal problems[d]	5.7 [11.4]	–	–	15.4 [24.0]	0.04[b]
n	28	–	–	47	
Pain in back and pelvis	20.8 [24.9]	16.0 [24.0]	13.3 [24.5]	16.0 [26.3]	0.02[a]
n	138	135	135	134	
Tingling/numbness	13.2 [25.3]	6.4 [19.3]	6.4 [18.9]	10.7 [24.4]	<0.001[a]
n	139	135	135	134	
Muscular pain	21.0 [27.6]	13.8 [26.2]	9.8 [23.1]	21.1 [30.5][c]	<0.001[a]
n	138	135	133	134	
Hair loss	3.8 [16.1]	3.2 [14.0]	4.9 [17.5]	5.4 [19.6]	0.5[a]
n	139	135	135	135	
Taste change	3.1 [12.7]	14.4 [27.7][c]	6.2 [20.4]	2.7 [14.2]	<0.001[a]
n	138	132	135	134	

Raw scores are transformed to 0–100 scale, and values represent mean scores [SD].
Higher scores on the functioning scale and the global QoL (GHS) scale indicate better functioning or QoL, whereas higher scores on the symptom scales represent a higher level of symptoms. A higher score on items related to sexuality (sexual interest, sexual activity and sexual enjoyment) indicate better sexual functioning.
RALH: robotic-assisted laparoscopic hysterectomy. GHS: global health status/quality of life.
[a] Mix effect model analysis indicating difference in values over time.
[b] Paired sample T test.
[c] Difference more than 10 points in comparison to previous observation (clinically significant).
[d] Only analysed for women who were sexual active (scored 2–4 on Q50).

functioning in EORTC C-30) at 1 and 5 weeks after surgery. These activities were resumed 4 months after surgery. Fatigue, pain, constipation, appetite and change of taste were negatively affected after surgery but returned to baseline levels at 5 weeks. We have previously conducted a qualitative study of women's experience of RALH for endometrial cancer [28]. We found that some women were surprised and troubled by

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Table 3
Scores of EQ-5D-3L.

Dimension	Levels	Baseline (n/%)	1 week (n/%)	5 weeks (n/%)	4 months (n/%)
Mobility	No problems	113 (81)	107 (77)	123 (89)[b]	113 (81)
	Problems	26 (19)	26 (19)	12 (9)[b]	22 (16)
Missing			6 (4)	4 (3)	4 (3)
Self-care	No problems	135 (97)	125 (90)	130 (94)	131 (94)
	Problems	4 (3)	9 (6)	5 (4)	4 (3)
Missing			5(4)	4 (3)	4 (3)
Usual activities	No problems	113 (81)	37 (27)[b]	89 (64)[b]	110 (79)[b]
	Problems	26 (19)	96 (69)[b]	46 (33)[b]	25 (18)[b]
Missing			6 (4)	4 (3)	4 (3)
Pain/discomfort	No problems	94 (68)	74 (53)[b]	105 (76)[b]	106 (76)
	Problems	45 (32)	60 (43)[b]	27 (19)[b]	28 (20)
Missing			5 (4)	7 (5)	5 (4)
Anxiety/depression	No problems	90 (65)	105 (76)[b]	104 (75)	103(74)
	Problems	49 (35)	29 (21)[b]	30 (22)	32 (23)
Missing			5 (4)	5 (4)	4 (3)
EQ VAS	1–100				
Mean [SD]		77 [20.5]	69 [23.1]	84 [18.7][b]	86 [16.8]
Missing		0	9	7	5
Mean difference from baseline (CI)		–	−9.2 (−12.8; −5.5)	7.1 (3.4; 10.7)	9.2 (5.5;12.8)
p value			<0.001[a]	<0.001[a]	<0.001[a]

[a] p value found by Linear Mixed Model analysis.
[b] More than 10% different from previous score.

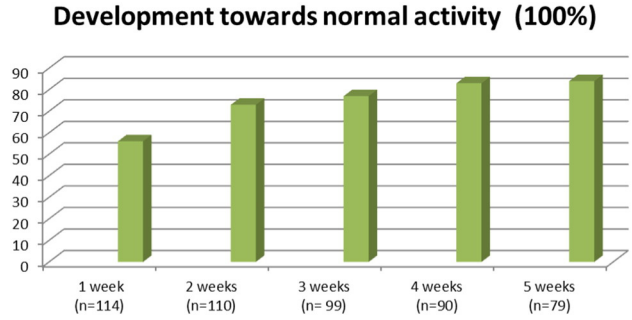

Fig. 2. Development towards normal activity.

fatigue and also by altered and painful bowel movements during the first postoperative weeks [28]. In the present study, we similarly found that loss of appetite and altered taste affected patients up to 5 weeks postoperatively. These unpleasant symptoms need attention during follow-up consultations. As no women in this sample received chemotherapy we were surprised by the number of women experiencing altered taste. Perioperative antibiotics, analgesics, other medication given during surgery or hormonal changes may be possible explanations. To our knowledge temporary change of taste has not been reported previously.

There was a clinically relevant increase in lymphedema from baseline to 4 months after surgery. Lymphedema is known to affect QoL negatively [29]. Considering that 22% of the women in the sample had pelvic lymphadenectomy (PLA) and that lymphedema develops over time [30], it is presumed that the incidence of lymphedema will continue to increase months after surgery. Our results did not indicate that women with PLA had a different development in HRQoL over the first 4 months measured by EQ-5D-3 L.

There are few studies of HRQoL, symptoms and function after RALH for endometrial cancer. We were not able to find studies examining short-term postoperative changes after RALH in HRQoL using validated illness specific questionnaires such as the EORTC EN-24. Lau and colleagues examined QoL in 109 women 21–28 days after RALH for endometrial cancer, however using a self-created questionnaire [31]. They reported that half of the women considered their QoL unchanged while 39% considered it improved [31]. Vaknin and colleagues studied 100 women with endometrial cancer undergoing RALH also using a self- constructed QoL questionnaire. They found that on a 5 point scale with 1 = much better, 2 = somewhat better, 3 = about the same, 4 = somewhat worse and 5 = much worse, the women rated their mean health status 4 weeks after surgery from 2.2–2.4 [32]. To enable meaningful comparison between studies, it is imperative that future research in gynaecologic oncology uses psychometrically robust and appropriate tools to assess patient-reported outcomes [4].

Sexual activity and interest were examined in a reduced sample. Therefore, we consider these findings explorative and primarily relevant for generating hypotheses for future studies. Sexual or vaginal problems appeared to increase from baseline to 4 months in sexually active women. For the majority, sexual interest and activity had declined after 4 months compared to baseline. Removal of the ovaries induces menopause, can worsen menopausal symptoms and affect HRQoL [33]. Oophorectomy affects sexual and vaginal health negatively, i.e. vulva/vaginal atrophy, vaginal discomfort, dryness, and dyspareunia, due to lack of hormones [34]. In addition, previous studies have shown that women are often dissatisfied with the quality and quantity of time health care professionals spend on addressing sexual life after gynaecological cancer treatment [35]. At follow-up in the outpatient clinic, health care professionals should engage in discussing sexual

Self-rated level of health		After 4 months						
		Very bad	Bad	Moderate	Good	Very good	missing	Total
Baseline	Very bad	0	2	0	0	0	0	2
	Bad	0	2	0	**3**	1	1	7
	Moderate	1	0	11	10	2	1	25
	Good	0	0	5	27	30	4	66
	Very good	0	2	2	11	20	2	37
	missing	0	0	1	0	1	0	2
	Total	1	6	19	51	54	8	139

Number in cells represents women. On the vertical level the baseline statement is read and on the horizontal the statement after 4 months is read. Example: **3 (bold)** women stated they rated their level of health at baseline as "*Bad*" but after 4 months they had changed to "*Good*".
The white diagonal cells captures patients that rated the same at baseline and after 4 months n=60 (43%)
Green colour indicates a better self-rated level of health within 4 months of RALH n= 48 (35%)
Red colour indicates worsened self-rated level of health within 4 months of RALH n=21 (15%) p= 0.001[a]
Missing N=10 (7%)
[a] Wilcoxon Signed Rank test

Fig. 1. Self-rated level of health.

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activity, including sexual problems and surgically induced anatomical changes.

Participants were asked to rate their self-perceived level of health on a single item question. This single item self-rated health question is a unique, valuable indicator of human health status [36]. By analysing the possible change over time we found that significantly more women reported improved rather than decreased health 4 months after RALH. We did not aim to predict a specific clinical outcome based on this single item question although the self-rated health question has been found to have a strong and constant association with mortality [36].

The level of activity increased gradually during the first 5 weeks after surgery. At 5 weeks, the mean level was 80% of the habitual level. In comparison Kornblich and colleagues found that regaining normal level of activity occurred slowly both for women treated by laparoscopy and even more so for women treated by laparotomy. After 6 weeks, the mean level of activity was 67% after laparoscopy and 57% after laparotomy [27].

In HRQoL studies, the occurrence of a response shift over time must be considered [37]. Response shift refers to the fact that there is a change in the meaning of one's self-evaluation of a target construct due to a change in internal standards of measurement, values, and redefinition of the target construct [37] — in other words a psychological adaption occurs. We cannot determine to what degree changes in scores are attributable to a response shift in the present study. However, we are aware that better scores may be the result of a response shift rather than of a change in condition. Therefore, the results should be interpreted with caution.

A strength of the study was the prospective cohort design and the use of a combination of validated generic and illness specific HRQoL questionnaires. For pragmatic reasons, baseline data was gathered in connection with planning of surgery. This may have affected baseline scores negatively if the women were concerned about the forthcoming surgery. Selection bias is an inherent risk in this type of study, as it is presumed that more resourceful women will participate — the healthy entrant effect [38]. This is consistent with our dropout analysis showing that women who were not included or excluded had more CVD and more had ASA 3. The high completion rate among participants is also a strength of this study. A limitation is the lack of data collection 2, 3, and 4 weeks after surgery. The women appeared to recover quickly after RALH. Therefore, these first weeks are relevant to monitor more closely in future studies in order to tailor follow-up.

We used repeated measurements with dependent data which increases statistical power because each individual acts as her own control. The advantage of using Linear Mixed Model is the ability to accommodate missing values (unbalanced data) [24]. This strengthens the results. An inherent limitation is the risk of a Type 1 error due to multiple testing [39].

Further research should focus on examining patient-reported function, symptoms and HRQoL weekly from 1 week to 8 weeks after surgery. Sexual issues after surgery should be explored further in more powerful studies. Selection bias should be prevented by encouraging more women to enrol. We believe we had a high rate of completers due to the fact that we interviewed women by telephone. By offering flexible choices for completion of questionnaires, for example face to face, electronically or by pen and paper with staff or on their own, even higher participation rates might potentially be achieved.

5. Conclusion

By using PROMs in clinical practice and in research, health care professionals can gain knowledge of the effects of disease and treatment on self-rated health, symptoms and functioning as perceived by patients. General health scores were above baseline at 5 weeks postoperatively, suggesting that RALH does not have a prolonged negative effect on general health. Fatigue, pain, constipation, gastrointestinal symptoms and appetite were negatively affected at 1 week but resolved at 5 weeks. Role functioning (performing work or hobbies) was reduced and altered taste persisted at 5 weeks postoperatively. Pre-surgery information and follow-up care programmes should address these issues. Four months postoperatively we found reduced sexual interest and activity and increased sexual or vaginal problems in sexually active women in a reduced sample. This warrants further investigation in larger studies with extended postoperative follow-up.

Conflicts of interest

No industry sponsorship and no conflicts of interest in connection with this article.

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Helbredsspørgeskema

Dansk version for Danmark

(Danish version for Denmark)

Angiv, ved at sætte kryds i én af kasserne i hver gruppe, hvilke udsagn, der bedst beskriver din helbredstilstand i dag.

Bevægelighed

Jeg har ingen problemer med at gå omkring ❑

Jeg har nogle problemer med at gå omkring ❑

Jeg er bundet til sengen ❑

Personlig pleje

Jeg har ingen problemer med min personlige pleje ❑

Jeg har nogle problemer med at vaske mig eller klæde mig på ❑

Jeg kan ikke vaske mig eller klæde mig på ❑

Sædvanlige aktiviteter *(fx.arbejde, studie, husarbejde, familie- eller fritidsaktiviteter)*

Jeg har ingen problemer med at udføre mine sædvanlige aktiviteter ❑

Jeg har nogle problemer med at udføre mine sædvanlige aktiviteter ❑

Jeg kan ikke udføre mine sædvanlige aktiviteter ❑

Smerter/ubehag

Jeg har ingen smerter eller ubehag ❑

Jeg har moderate smerter eller ubehag ❑

Jeg har ekstreme smerter eller ubehag ❑

Angst/depression

Jeg er ikke ængstelig eller deprimeret ❑

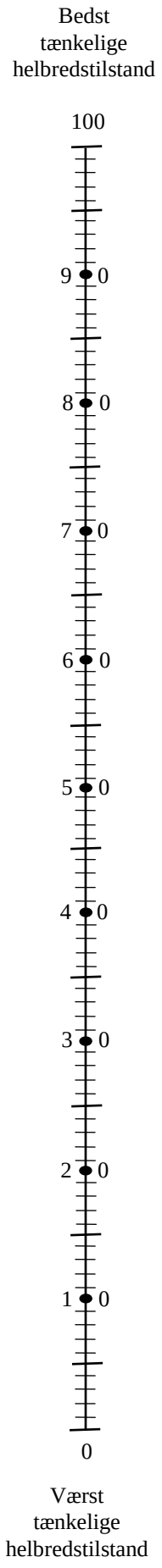
Jeg er moderat ængstelig eller deprimeret ❑

Jeg er ekstremt ængstelig eller deprimeret ❑

For at hjælpe folk med at sige, hvor god eller dårlig en helbredstilstand er, har vi tegnet en skala (næsten ligesom et termometer), hvor den bedste helbredstilstand du kan forestille dig er markeret med 100, og den værste helbredstilstand du kan forestille dig er markeret med 0.

Vi beder dig angive på denne skala, hvor god eller dårlig du mener din egen helbredstilstand er i dag. Angiv dette ved at tegne en streg fra kassen nedenfor til et hvilket som helst punkt på skalaen, der viser, hvor god eller dårlig din helbredstilstand er i dag.

Din egen helbredstilstand i dag



EORTC QLQ-C30 (version 3.0)

Vi er interesserede i at vide noget om dig og dit helbred. Vær venlig at besvare alle spørgsmålene selv ved at sætte en ring omkring det svar (tal), som passer bedst på dig. Der er ingen "rigtige" eller "forkerte" svar. De oplysninger, som du giver os, vil forblive strengt fortrolige.

Skriv venligst dine forbogstaver her: |_|_|_|_|
Din fødselsdato (dag, måned, år): |_|_|_|_|_|_|_|_|
Dato for udfyldelse af dette skema (dag, måned, år): 31 |_|_|_|_|_|_|_|_|

		Slet ikke	Lidt	En del	Meget
1.	Har du nogen vanskeligheder ved at udføre anstrengende aktiviteter, som f.eks. at bære en tung indkøbstaske eller en kuffert?	1	2	3	4
2.	Har du nogen vanskeligheder ved at gå en lang tur?	1	2	3	4
3.	Har du nogen vanskeligheder ved at gå en kort tur udendørs?	1	2	3	4
4.	Er du nødt til at ligge i sengen eller at sidde i en stol om dagen?	1	2	3	4
5.	Har du brug for hjælp til at spise, tage tøj på, vaske dig eller gå på toilettet?	1	2	3	4

I den forløbne uge:

		Slet ikke	Lidt	En del	Meget
6.	Var du begrænset i udførelsen af enten dit arbejde eller andre daglige aktiviteter?	1	2	3	4
7.	Var du begrænset i at dyrke dine hobbyer eller andre fritidsaktiviteter?	1	2	3	4
8.	Havde du åndenød?	1	2	3	4
9.	Har du haft smerter?	1	2	3	4
10.	Havde du brug for at hvile dig?	1	2	3	4
11.	Har du haft besvær med at sove?	1	2	3	4
12.	Har du følt dig svag?	1	2	3	4
13.	Har du savnet appetit?	1	2	3	4
14.	Har du haft kvalme?	1	2	3	4
15.	Har du kastet op?	1	2	3	4

Vær venlig at fortsætte på næste side

I den forløbne uge:

	Slet ikke	Lidt	En del	Meget
16. Har du haft forstoppelse?	1	2	3	4
17. Har du haft diarré (tynd mave)?	1	2	3	4
18. Var du træt?	1	2	3	4
19. Vanskeliggjorde smerter dine daglige gøremål?	1	2	3	4
20. Har du haft svært ved at koncentrere dig om ting som f.eks. at læse avis eller se fjernsyn?	1	2	3	4
21. Følte du dig anspændt?	1	2	3	4
22. Var du bekymret?	1	2	3	4
23. Følte du dig irritabel?	1	2	3	4
24. Følte du dig deprimeret?	1	2	3	4
25. Har du haft svært ved at huske?	1	2	3	4
26. Har din fysiske tilstand eller medicinsk behandling vanskeliggjort dit familieliv?	1	2	3	4
27. Har din fysiske tilstand eller medicinsk behandling vanskeliggjort din omgang med andre mennesker?	1	2	3	4
28. Har din fysiske tilstand eller medicinsk behandling medført økonomiske vanskeligheder for dig?	1	2	3	4

Ved de næste 2 spørgsmål bedes du sætte en ring omkring det tal mellem 1 og 7, som passer bedst på dig

29. Hvordan vil du vurdere dit samlede helbred i den forløbne uge?

1 2 3 4 5 6 7

Meget dårligt Særdeles godt

30. Hvordan vil du vurdere din samlede livskvalitet i den forløbne uge?

1 2 3 4 5 6 7

Meget dårlig Særdeles god

EORTC QLQ – EN24

Patienter fortæller undertiden, at de har følgende symptomer eller problemer. Anfør venligst, i hvilket omfang du har haft disse symptomer eller problemer.

I den forløbne uge:		Slet ikke	Lidt	En del	Meget
31.	Har du haft hævelser i ét eller begge ben?	1	2	3	4
32.	Har du følt tyngde i ét eller begge ben?	1	2	3	4
33.	Har du haft smerter i lænden og / eller bækkenet?	1	2	3	4
34.	Når du følte trang til at lade vandet, skulle du så skynde dig på toilettet?	1	2	3	4
35.	Har du haft hyppig vandladning?	1	2	3	4
36.	Har du haft svært ved at holde på vandet (ufrivillig vandladning)?	1	2	3	4
37.	Har du haft smerter eller svie under vandladningen?	1	2	3	4
38.	Når du skulle have afføring, skulle du så skynde dig på toilettet?	1	2	3	4
39.	Har du haft svært ved at holde på afføringen?	1	2	3	4
40.	Har du været generet af rigelig tarmluft?	1	2	3	4
41.	Har du haft mavekramper?	1	2	3	4
42.	Har du følt dig oppustet i maven?	1	2	3	4
43.	Har du haft stikken/prikken eller nedsat følsomhed i hænder eller fødder?	1	2	3	4
44.	Har du haft ømhed eller smerter i muskler eller led?	1	2	3	4
45.	Har du haft hårtab?	1	2	3	4
46.	Har mad og drikke smagt anderledes end normalt?	1	2	3	4

Gå venligst videre til næste side

I den forløbne uge:		**Slet ikke**	**Lidt**	**En del**	**Meget**
47.	Har du følt dig mindre fysisk tiltrækkende på grund af din sygdom eller behandling?	1	2	3	4
48.	Har du følt dig mindre feminin på grund af din sygdom eller behandling?	1	2	3	4

I de sidste 4 uger:		**Slet ikke**	**Lidt**	**En del**	**Meget**
49.	I hvilket omfang har du haft lyst til seksuelt samvær?	1	2	3	4
50.	I hvilket omfang har du været seksuelt aktiv?	1	2	3	4
	Besvar kun disse spørgsmål, hvis du har været seksuelt aktiv indenfor de sidste 4 uger:	1	2	3	4
51.	Følte du at din skede var tør ved seksuelt samvær?	1	2	3	4
52.	Har din skede føltes kort og/eller snæver?	1	2	3	4
53.	Har du haft smerter ved samleje eller andet seksuelt samvær?	1	2	3	4
54.	Nød du det seksuelle samvær?	1	2	3	4