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

Suzanne Forsyth Herling

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Tutor(s): Ann Møller, Thordis Thomsen & Connie Palle

Official opponents: Lis Adamsen, Erik Elgaard Sørensen & Henrik Falconer

Correspondence: Department of Anaesthesiology, Herlev and Gentofte Hospital, University of Copenhagen

E-mail: suzanne.herling@gmail.com

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1. LISTS OF PAPERS

The PhD thesis is based on the following four original papers:

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PAPER II
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Authors: Herling SF, Møller AM, Palle C, Thomsen T.

2. 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 % myo-invasion 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, Copenhagen University Hospital, Herlev

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 Copenhagen University Hospital, Herlev, 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 Copenhagen University Hospital, Herlev, was established. The Centre is a collaboration between the department of Urology, Gastroenterology and Gynaecology who all use the three available surgical robots.

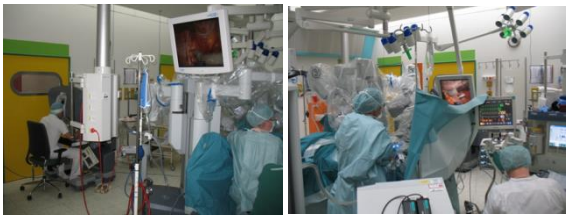

Figure 1. Robotic-assisted laparoscopic hysterectomy performed at Copenhagen University Hospital, Herlev.

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 Copenhagen University Hospital, Herlev 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 Copenhagen University Hospital, Herlev 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 antithrombotic stockings during the entire hospital stay.
After surgery, the women were monitored in the Post-anesthetic 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.)

3. 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, postoperative nausea and vomiting (PONV), immobilisation, bleeding and impaired urinary or gastrointestinal functioning as well as psycho-social reactions to surgery in due time.

4. 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).

5. 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).

6. 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).

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 1
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.

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.

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.

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.

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.

7. 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 post-operative 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).

8. 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.

9. IMPLICATIONS FOR PRACTICE AND 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.

10. 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.

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APPENDIX 1

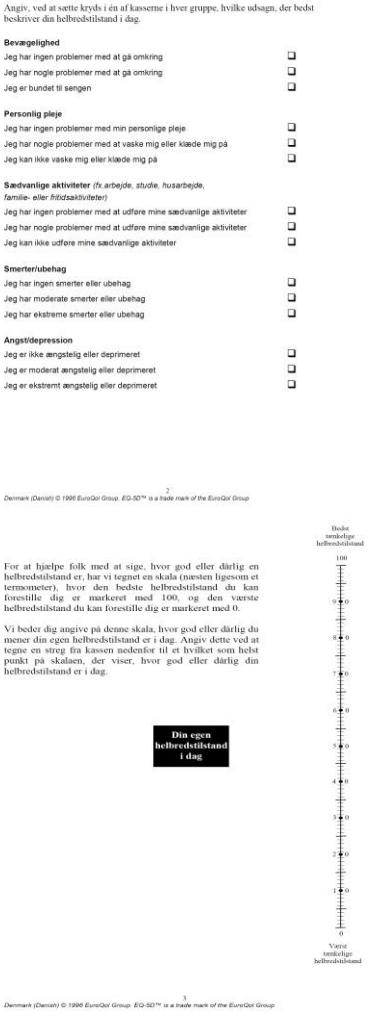
Clavien-Dindo score

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)

Appendix 6



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 ☐

2
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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

Bedst tænkelige helbredstilstand
100
90
80
70
60
50
40
30
20
10
0
Værst tænkelige helbredstilstand

3
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Appendix 7

DANISH

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

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
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

DANISH informal

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