On Quality Improvement in Gynaecological Cancer Surgery

with emphasis on perioperative outcome, recovery and health economics

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In memory of my parents,

Elise Cécile Snijders († 2015) and Rudolphe Serreyn († 2017)

"Science is at no moment quite right, but it is seldom quite wrong, and has, as a rule, a better chance of being right than the theories of the unscientific. It is, therefore, rational to accept it hypothetically”

Russel, B. (1959)
Abstract

Objectives: The overall purpose of this thesis was to find medical and surgical treatment methods of improving the perioperative care of gynaecological cancer patients. The specific objectives were to determine whether a single dose tranexamic acid given immediately before surgery for presumed advanced ovarian cancer reduces perioperative blood loss and the need for blood transfusions, and to determine whether postoperative recovery, tissue damage, and inflammatory response markers differ between women operated with robotic and abdominal hysterectomy for low-risk endometrial cancer in an enhanced recovery after surgery (ERAS) programme, and to evaluate costs for hospital stay and postoperative recovery in relation to health impact.

Material and Methods: The thesis was based on two randomised trials. The first trial was a randomised double-blind placebo-controlled multicentre study conducted in four hospitals in the southeast and central of Sweden between March 2008 and May 2012. One hundred women with presumed advanced ovarian cancer who had been scheduled for radical debulking surgery were included; 50 received tranexamic acid and 50 received a placebo. The main outcomes were blood loss and red blood cell transfusions. The second trial was a randomised open single centre trial at a Swedish university hospital, which included 50 women with low-risk endometrial cancer scheduled for radical surgery between February 2012 and May 2016; 25 women underwent robotic hysterectomy and 25 had abdominal hysterectomy. Anaesthesia and perioperative care followed an ERAS protocol in both groups. The EuroQol Group form EQ-5D-3L and the Short Form-36 evaluated the health-related quality of life. The Swedish Postoperative Symptoms Questionnaire assessed symptoms perioperatively until six weeks postoperatively. Venous blood samples were collected on several occasions until six weeks postoperatively and were analysed for markers reflecting inflammatory response and tissue damage. In addition, a health-economy analysis was conducted comparing total costs, quality-adjusted life years (QALYs) and cost per QALY between the surgical methods.

Results: Total blood loss volume and transfusion rate following surgery in advanced ovarian cancer were significantly lower in the tranexamic group compared with the placebo group. Women with early endometrial cancer treated by robotic hysterectomy recovered significantly faster in the EQ-5D health index, and reached their preoperative level nearly two weeks earlier than the abdominal group. Differences regarding improvement in health-related quality of life (Short Form-36) comprising general health and social functioning were more favourable in the robotic hysterectomy group. Consumption of analgesics, pain intensity, postoperative symptom sum score and length of hospital stay were equal between the groups. The occurrence of complications was an independent risk factor and influenced most of the outcome measures adversely. Postoperative inflammatory response and tissue damage were lower after robotic hysterectomy compared with the abdominal approach. The robotic group gained more QALYs until six weeks after surgery than the abdominal group but the total costs were higher. The total cost per QALY gained was quite high for the robotic procedure.
Conclusions: A single dose of tranexamic acid given immediately before surgery reduces blood loss and transfusion rates in advanced ovarian cancer surgery. Robotic hysterectomy in an ERAS programme treating early endometrial cancer leads to a faster recovery in the health-related quality of life than abdominal hysterectomy, the latter being strongly influenced by perioperative complications. Less tissue damage and inflammation might contribute to a faster recovery in the robotic group. Robotic hysterectomy provides more QALYs until six weeks postoperatively but with a substantially higher total cost for the society.
List of scientific papers

I. Single-dose tranexamic acid in advanced ovarian cancer surgery reduces blood loss and transfusions: double-blind placebo-controlled randomized multicenter study
Evelyn Serreyn Lundin, Torsten Johansson, Helene Zachrisson, Ulf Leandersson, Fatma Bäckman, Laila Falknäs, Preben Kjølhede. Acta Obstet Gynecol Scand. 2014;93(4):335-44.

II. A prospective randomized assessment of quality of life between open and robotic hysterectomy in early endometrial cancer
Evelyn Serreyn Lundin, Ninnie Borendal Wodlin, Lena Nilsson, Preben Kjølhede. Int J Gynecol Cancer. 2019 Mar;DOI:10.1136/ijgc-2019-000285.

III. Markers of tissue damage and inflammation after robotic and abdominal hysterectomy in early endometrial cancer: a randomized controlled trial
Evelyn Serreyn Lundin, Ninnie Borendal Wodlin, Lena Nilsson, Elvar Theodorsson, Jan Ernerudh, Preben Kjølhede. Submitted.

IV. Cost-effectiveness of robotic hysterectomy versus abdominal hysterectomy in early endometrial cancer
Evelyn Serreyn Lundin, Per Carlsson, Ninnie Borendal Wodlin, Lena Nilsson, Preben Kjølhede. Submitted.

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**Abbreviations**

AH | Abdominal hysterectomy
ANOVA | Analysis of variance
ASA | American Society of Anesthesiologists
BMI | Body mass index
CHEERS | Consolidated health economic evaluation reporting standards checklist
CI | Confidence interval
CK | Creatine kinase
CONSORT | Consolidated standards of reporting trials
DDD | Defined daily dose
EQ-5D-3L | EuroQoL-5dimensions-3levels questionnaire
ERAS | Enhanced recovery after surgery
FIGO | International Federation of Gynecology and Obstetrics
HADS | Hospital anxiety and depression scale
Hb | Haemoglobin
HMGB1 | High-mobility group box 1 protein
HR | Hazard ratio
HRQoL | Health-related quality of life
hsCRP | High-sensitivity C-reactive protein
ICER | Incremental cost-effectiveness ratio
IL-6 | Interleukin-6
MCS | Mental component summary score
NSAID | Nonsteroidal anti-inflammatory drugs
OR | Odds ratio
PACU | Post anaesthesia care unit
PBV | Predicted blood volume
PCS | Physical component summary score
PSQ | Pain sensitivity questionnaire
QALY | Quality-adjusted life years
RBC | Red blood cells
RCT | Randomised controlled trial
RH | Robotic hysterectomy
SD | Standard deviation
SF-36 | Short Form Health Survey
SPSQ | Swedish postoperative symptoms questionnaire
WBC | White blood cells
WHO | World Health Organization
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Introduction

Surgery is a cornerstone in the treatment of gynaecological cancer (Giede, et al. 2013, Narasimhulu, et al. 2015, Dellinger, et al. 2017, Swailes, et al. 2017). The surgery impacts quality of life in general, not only in the postoperative period but also in the long term, with effects on prognosis and consequently cancer survival. Therefore, it is important to constantly investigate methods that can lead to medical and surgical improvements in the care of women undergoing gynaecological cancer surgery.

During the last century, many efforts have been made to develop surgical techniques and perioperative care programmes in order to improve recovery after surgery. In the 1920s, the idea of controlling blood loss by heat, used for many thousands of years, led to the development of electrosurgical instruments with the ability to control bleeding during surgical procedures (Vellimana, et al. 2009). Today electrosurgery has evolved into modern bipolar technology, comprising various coagulation instruments, and has the potential to improve outcomes perioperatively.

In the late 1980s, a shift occurred from open abdominal surgery to minimally invasive techniques such as laparoscopy. This mode of operation had already been introduced in 1901 but gained renewed interest in the 80s due to technical improvements (Vecchio, et al. 2000). The most recent of the technical developments is the advanced robot-assisted surgical system. The first documented use of robot-assisted surgical equipment occurred in 1985 when the PUMA 560 robotic surgical arm was used in a delicate neurosurgical biopsy, a non-laparoscopic surgery. The worldwide distribution and breakthrough of robotic surgery came in 2000 when the da Vinci Surgical System was approved by the US Food and Drug Administration for general laparoscopic surgery. By the introduction of this robotic system many challenges of conventional laparoscopy were overcome, and the technique was rapidly adopted. Strong marketing possibly played a role in its rapid spread (Mok, et al. 2012, Liu, et al. 2014).

Even perioperative care has developed over the years. Today, enhanced recovery after surgery (ERAS) is a well-documented perioperative care programme using the best evidence-based treatment for each perioperative element to reduce hormonal surgical stress response and achieve enhanced recovery without increasing complications and the readmission rate (Ljungqvist, et al. 2017). It started as a perioperative protocol for patients undergoing colonic surgery, and led to a shorter length of hospital stay, and improved recovery with fewer postoperative complications (Greco, et al. 2014). The programme is now implemented in different surgical specialties in many countries. The first international ERAS guidelines for gynaecological surgery were established in 2016 (Nelson, et al. 2016a, Nelson, et al. 2016b) and these programmes also recommend the use of minimally invasive surgery when possible. Although robot-assisted laparoscopic surgery has become more widespread in gynaecological cancer surgery, the procedure has not been evaluated in well-conducted high evidence-level trials. Only a few randomised trials for endometrial cancer comparing robotic with open surgery, rarely using an ERAS model, have been published (Wijk, et al. 2016, Salehi, et al. 2018).
The clinical benefits of the robotic technique are still being debated in relation to the increased costs of acquisition and maintenance of the equipment (Kristensen, et al. 2017). Health economic evaluations are needed to compare both the costs and effectiveness before acceptance and implementation of new treatments improving perioperative management and recovery in clinical practice. Calculating the costs of alternative treatments to quantify the health-related quality-adjusted life years gained (QALYs) is important because this enables comparison of cost-effectiveness within and between disease groups.

This thesis is based on two randomised controlled trials concerning surgery of gynaecological cancers. The first trial, the so-called “Cyklokapron study” (“Tranexamic acid (Cyklokapron®) in surgery for advanced ovarian cancer – a prospective randomised double-blind placebo-controlled multicentre study”) was carried out to determine if the perioperative management of women with advanced ovarian cancer could be improved by giving the drug tranexamic acid immediately before surgery in order to minimise blood loss during surgery and reduce the need for blood transfusions.

In the second trial, the so-called “Robothyst study” (“Robot-assisted laparoscopic hysterectomy versus abdominal hysterectomy in an ERAS programme in endometrial cancer – an open randomised controlled trial), we examined whether the management of women with early endometrial cancer in an ERAS programme could be improved using robot-assisted laparoscopic surgery compared to conventional open abdominal surgery in terms of a faster postoperative recovery and less tissue damage, and whether robotic surgery was more advantageous health-economically.
Background

Ovarian cancer surgery and blood loss

The majority of women with ovarian cancer are diagnosed at an advanced tumour stage, namely the International Federation of Gynecology and Obstetrics (FIGO) stage IIIC-IV (Appendix 1). Currently, the recommended standard treatment of women with advanced epithelial ovarian cancer is radical surgery followed by platinum-based chemotherapy (www.cancercentrum.se). Treatment may be started with neoadjuvant chemotherapy if the surgery is considered not to be able to achieve radicality macroscopically. After three or four courses of chemotherapy a delayed primary surgery can be performed, followed by the remaining courses of chemotherapy.

The goal of the surgery is to remove all of the visible tumour, called debulking or cytoreductive surgery. After the operation, chemotherapy is given to treat residual tumour or microscopic disease. It is well-documented that optimal primary debulking surgery is crucial for the survival and recurrence rate in advanced ovarian cancer (Ang, et al. 2011, Elattar, et al. 2011, Chang, et al. 2013). The cytoreductive surgery is often extensive, encompassing omentectomy, resection of parietal and visceral peritoneum, the diaphragm, bowels and other abdominal organs, with a risk of excessive bleeding frequently exceeding 1,000 ml as extensive intra-abdominal metastases are typical for advanced ovarian cancer. Approximately 40% of women with ovarian cancer undergoing extensive surgery require blood transfusions (Abu-Rustum, et al. 2005). Excessive blood loss following surgery increases morbidity and mortality but also delays the recovery. The indication for the administration of blood products in surgery is basically to improve tissue oxygen delivery and thereby provide optimal conditions for physical recovery. Blood products are a scarce resource and a blood transfusion is associated with certain risks. Twenty percent of all blood transfusions result in adverse events, with serious complications occurring in about 0.5% of cases (Delaney, et al. 2016).

The more common complications are localised or systematic allergic transfusion reactions, haemolytic reactions with and without fever and transfusion-associated cardiac overload. Other complications are more seldom seen, but include infectious pathogen transmission, when an emerging infectious agent is identified as a risk to the blood supply, and transfusion-related acute lung injury with often fatal pulmonary oedema. By transfusion-related immune modulation, perioperative blood transfusions have been shown to increase the risk of bacterial infections after the operation and also cause an increased risk of cancer recurrence with a reduced survival rate after optimal cytoreductive or curative operation (De Oliveira, et al. 2012, Schiergens, et al. 2015, Cybulski, et al. 2017). Perioperative blood transfusions are likewise associated with an increased risk of venous thromboembolism, and higher composite morbidity, mortality, and length of hospital stay (Prescott, et al. 2015).
Tranexamic acid (Cyklokapron®)

Surgery or tissue trauma physiologically triggers activation of the haemostatic or blood clotting system. Initially, the formation of thrombin stimulates the conversion of fibrinogen into fibrin. The fibrinolytic processes are subsequently activated to break down the fibrin clot in order to maintain vascular patency. Fibrinolysis begins after the conversion of plasminogen into plasmin, an enzyme necessary for the breakdown of fibrin. Plasmin formation is stimulated by tissue plasminogen activator and urokinase plasminogen activator, which are endogenous activators of plasminogen. Plasmin activity is also modulated by various naturally occurring plasminogen activator inhibitors to achieve a balance between clot formation and breakdown (McCormack 2012). Although fibrinolysis is part of the normal physiological response to tissue trauma, any disturbance in the balance between activators and inhibitors of the fibrinolytic system may result in excessive bleeding. During surgery, increased activity of plasminogen also increases the consumption of the plasminogen activator inhibitor and in turn the premature breakdown of fibrin. In procedures that result in extensive tissue damage, this process may be excessive and can result in a state of hyperfibrinolysis, with bleeding as a result. Tranexamic acid works by preventing the breakdown of blood clots and so reduces bleeding. The process of clot formation and degradation, and the effect of tranexamic acid are illustrated in Figure 1.

![Figure 1. Effect of tranexamic acid on plasminogen and fibrin degradation.](image)

Since the introduction of tranexamic acid into clinical practice in the early 1960s, the drug has been used in a wide variety of surgical and trauma settings to treat or significantly prevent excessive blood loss. A number of systematic reviews have reported on the perioperative administration of tranexamic acid with the aim of reducing blood loss and the need for blood transfusion. It is a commonly used drug in obstetrics to treat postpartum haemorrhage (Novikova, et al. 2015, WOMAN Trial Collaborators 2017) and bleeding following caesarean section (Franchini, et al. 2018); in gynaecology it is mostly used to treat menorrhagia...
(Bradley and Gueye 2016) and in gynaecological surgery it has been shown to be an effective intervention to reduce blood loss during myomectomy for fibroids when compared with placebo (Kongnyuy and Wiysonge 2014). In orthopaedic surgery tranexamic acid has been used successfully to reduce perioperative blood loss, particularly in total hip and knee arthroplasty and spine surgery (Bai, et al. 2019, Kamatsuki, et al. 2019, Xie, et al. 2019). Tranexamic acid has been shown to reduce the risk of death due to bleeding by 15% in trauma patients (Roberts 2015). Moreover, in cardiac surgery tranexamic acid has been seen to have positive effects on blood loss and the blood transfusion rate (Gerstein, et al. 2017).

In surgical oncology only a few studies have analysed the effect of prophylactic tranexamic acid. In urology one study has examined intraoperative treatment with low-dose tranexamic acid in patients undergoing prostatectomy for prostate cancer, and this showed a reduced intraoperative blood loss with no increase in the rate of thromboembolic events at six months’ follow-up (Crescenti, et al. 2011). In urinary bladder cancer surgery a randomised trial is ongoing in Canada (Breau, et al. 2018). In abdominal tumour surgery a small RCT has shown that a bolus dose of tranexamic acid followed by an infusion that was continued for four hours postoperatively, gave a more effective reduction of postoperative blood loss compared with a single bolus dose given intravenously (Prasad, et al. 2018).

Yet, tranexamic acid given as prophylaxis is still not considered as a standard of care. The evidence for serious adverse events such as thromboembolic events and mortality, and effects in the treatment of high-risk women, is still insufficient to draw conclusions about safety although no such increased risk has been demonstrated in existing clinical trials (Perel, et al. 2013, Lin and Woolf 2016, Franchini, et al. 2018). Even the optimal dose and dosing regimens have not been sufficiently analysed. In cardiac surgery a dose-dependent relationship was seen between the dose of tranexamic acid and the incidence of seizures (Myles, et al. 2017, Takagi, et al. 2017). It seemed that doses above 100 mg/kg resulted in an increased incidence of this adverse effect. The underlying mechanism is not fully understood but a receptor in the brain is being discussed.

From a health economic point of view, tranexamic acid is interesting. The direct cost of one unit of Red Blood Cells (RBC) is about SEK 1,500, which is expensive compared to the cost of a single dose of 1.5 gram tranexamic acid for intravenous use, which is about SEK 100.

Within gynaecological cancer surgery data are scarce on the preventive effect of tranexamic acid on blood loss and blood transfusion requirements (Celebi, et al. 2006). It is clinically interesting to analyse whether a similar positive effect as seen in other surgical areas can be achieved in cytoreductive surgery for advanced ovarian cancer and whether this could improve the care of women with ovarian cancer.

**Perioperative care and ERAS**

Perioperative care is the care given from the decision on surgery until full recovery after the operation, and its aim is to improve the patient outcome. The understanding that the entire process around the operation was important to achieve and enhance recovery became more apparent when Professor Henrik Kehlet from Denmark introduced the principles of fast track
or multimodal surgical care in abdominal surgery in the early 1990s (Kehlet 1997). The purpose of these multimodal strategies was to reduce the perioperative stress response and improve postoperative recovery following elective surgery (Kehlet and Wilmore 2002). Symptoms like nausea, vomiting, headache, abdominal pain, impaired bowel function, tiredness and drowsiness contribute to postoperative morbidity, length of hospital stay and slow postoperative recovery. A multimodal approach to avoid and minimise these symptoms was therefore seen as essential.

Inspired by the pivotal work of Henrik Kehlet the ERAS® Study Group was founded in 2001 by clinicians from Sweden, Norway, Denmark, the UK and the Netherlands (Ljungqvist, et al. 2017) with the aim of discussing multimodal surgical care. The group proposed guidelines for multimodal surgical care but noted that none of the participating countries actually followed these recommendations of evidence-based care (Lassen, et al. 2005). Then, the first ERAS consensus protocol was published in 2005 for patients undergoing colonic surgery, and later also for rectal surgery patients, with an update in 2013 (Gustafsson, et al. 2013, Nygren, et al. 2013). More recent studies about ERAS in colorectal surgery have shown reduced length of hospital stay without compromising the quality of care, and reduced postoperative morbidity and mortality (Gustafsson, et al. 2016).

The ERAS® Society, an international extension of the ERAS® Study Group, was officially founded in 2010 in Stockholm, Sweden with the mission “to develop perioperative care and to improve recovery through research, education, audit and implementation of evidence-based practice” (www.erassociety.org). New guidelines have been established for a variety of specialties (Visioni, et al. 2018). The continuously updated recommendations differ slightly between the procedures but the main principles are the same.

In gynaecological surgery from the 1990s onwards, occasional trials have been published including some of the ERAS principles with the objective of shortening hospital stay for women with benign and malignant disease (Rardin, et al. 1999, Ghosh, et al. 2001). Then a number of prospective cohort studies with the concept “fast track”, later called ERAS, were published all showing short hospital stay, one day for laparoscopic hysterectomy and two days for abdominal hysterectomy (Moller, et al. 2001), and a reduction of two hospital days with fewer complications for ovarian cancer patients (Marx, et al. 2006, Carter 2012). More trials followed with ERAS in gynaecology covering benign and oncological surgery (Chapman, et al. 2016, de Groot, et al. 2016, Kalogera and Dowdy 2016).

An ERAS programme consists of several parts and includes preoperative education of the patient that provides clear information concerning pre-, peri- and post-operative care, use of safe and short-acting anaesthetics, use of minimally invasive surgery when feasible, optimisation of postoperative pain relief comprising use of local and regional anaesthetic (spinal anaesthesia with intrathecal morphine or epidural anaesthesia), minimal use of opioids, optimal nausea treatment, early start of enteral nutrition, early ambulation, and balanced perioperative fluid regulation (Nelson, et al. 2016a, Nelson, et al. 2016b). The programme visualises the patient’s pathway through surgery until recovery and emphasises the involvement of the entire surgical and anesthesiological team as well as the nursing staff in order to obtain the potential advantages of the ERAS model for postoperative recovery, as shown in Figure 2.
Figure 2. ERAS principles in different phases of the perioperative course.

The ERAS programmes recommend the use of minimally invasive surgery when possible because of the clinical benefits including faster recovery and fewer infections (Galaal, et al. 2012). There are limited data about ERAS and robotic surgery even when the use of an ERAS programme gives a unique opportunity to treat the patients similarly aside from the studied surgical treatment method (Kalogera, et al. 2019). This was also one of the reasons why we wanted to investigate if robotic surgery in an ERAS programme, compared with abdominal surgery, could contribute to improved care of women with early endometrial cancer.

### Tissue damage and recovery

Tissue damage and inflammation after surgery, involving several cascades of reactions, are important factors thought to affect postoperative recovery (Desborough 2000). The biological reactions have been studied in part, but much is still unknown about what affects recovery. Surgical tissue trauma is a physical and psychological stressing condition that triggers a systemic response regulated by a complex network of endocrine, neural and immunological mechanisms. The stress response leads to increased sympathetic nervous activity with elevated secretion of catecholamines and glucocorticoids as well as an early increase of inflammatory mediators essential for tissue repair and immunological defence. The response also provokes alterations of both cellular and humoral immunity resulting in transient immunosuppression (Moselli, et al. 2011). The overall metabolic effect of the hormonal changes is increased catabolism which mobilises substrates to provide energy sources, and a mechanism to retain water and salt in order to maintain fluid volume and cardiovascular homeostasis.

The ERAS programmes include measures to reduce these undesirable effects by using afferent neural blockade with regional anaesthesia and the use of carbohydrate loading preoperatively, counteracting the development of insulin resistance and minimising protein loss, thereby improving postoperative outcome and recovery (Wilmore 2002).
Tissue damage and inflammatory response can be expressed and measured by changes in circulating levels of pro-inflammatory cytokines, inflammatory proteins, immunological cells, stress hormones and tissue damage markers.

The most studied pro-inflammatory cytokine in surgery is interleukin-6 (IL-6) (Brocker, et al. 2010). The term ‘interleukin’ has been used to describe a group of cytokines that were first seen to be expressed by white blood cells and that have complex immunomodulatory functions. Determining the exact function of a particular cytokine is complicated by the influence of the producing cell type, the responding cell type and the phase of the immune response. Interleukins can also have pro- and anti-inflammatory effects, further complicating their characterisation. Cytokines play an important role in nearly all aspects of inflammation and immunity (Brocker, et al. 2010).

The classical acute phase reactant is C-reactive protein (CRP) synthesised by the liver. The concentration of the marker rises rapidly and extensively in a cytokine-mediated response to tissue injury, infection and inflammation. Serum CRP levels are routinely measured to detect and monitor many diseases. However, CRP is likely to have important host defence, cleansing and metabolic functions, and can also activate the classical complement pathway (Thompson, et al. 1999). Traditionally, CRP is measured down to concentrations of 3 to 5 mg/L; high-sensitivity C-reactive protein (hsCRP) is measured down to concentrations of approximately 0.3 mg/L.

Surgical trauma is associated with a stress response that varies in accordance with the nature and degree of tissue damage (Khoo, et al. 2017). Critical to this response is the release of cortisol, mediated by the hypothalamic-pituitary-adrenal axis. The effects of cortisol in the setting of surgical stress are complex, but include the suppression of insulin and the mobilisation of energy stores by gluconeogenesis and glycogenolysis, increased proteolysis, sodium and water retention leading to preservation of blood pressure, suppression of the immune inflammatory response, and delayed wound healing through its effects on collagen synthesis (Plumpton and Besser 1969).

One of the most proposed indirect indicators of muscle damage is serum creatine kinase (CK), due to its ease of identification and the relatively low cost of assays to quantify it (Kumbhare, et al. 2008). Three cytoplasmic isoforms of CK have been identified: CK-MM, which is a marker of myopathies; CK-MB, which rises after acute myocardial infarction; and CK-BB which is released in brain damage (Koch, et al. 2014).

Another marker for tissue damage is high-mobility group box 1 protein (HMGB1). This is a nuclear protein that is released following trauma or severe cellular stress. The HMGB1 release is caused by cytokines, activated complement and hypoxia. Extracellular HMGB1 triggers inflammation and recruits leukocytes to the site of tissue damage (Venereau, et al. 2013).

The systemic stress response to surgery is shown in Figure 3. The magnitude of this reaction is linked to the severity of the tissue trauma (Watt, et al. 2015). Some studies have shown that minimally invasive hysterectomy (vaginal or by laparoscopy) causes less tissue damage than abdominal hysterectomy (Harkki-Siren, et al. 2000, Malik, et al. 2001, Ribeiro, et al. 2003, Yue, et al. 2009, Oksuzoglu, et al. 2015). Other studies have shown significantly different immunological responses depending on the mode of hysterectomy and anaesthesia with a lower inflammatory response, and better influence on cellular immunity of laparoscopic
hysterectomy compared with the open approach (Valien, et al. 2007, Hong and Lim 2008, Yue, et al. 2009). It is uncertain whether these differences in inflammatory and immunological response remain in an ERAS programme with the use of spinal anaesthesia with intrathecal morphine as postoperative analgesia and it is not clear how less tissue trauma contributes to a faster recovery.

**Figure 3.** Systemic responses to surgery: sympathetic nervous system activation, endocrine ‘stress response’ with pituitary hormone secretion and insulin resistance, immunological and haematological changes with cytokine production, acute phase reaction, leucocytosis, lymphocyte proliferation, and whole body protein catabolism. Reprinted with permission (Gillis and Carli 2015).

**Robotic surgery**

The idea of using robotics for surgery was proposed as far back as 1967, but it took nearly 30 years to complete the first fully functional multipurpose surgical robot. Originally, the development was started in the 1970s by the US National Aeronautics and Space Administration (NASA) which was interested in remote surgery or tele surgery and its application for astronauts in orbit. Simultaneously, the US Defence Advanced Research Project Agency (DARPA) developed plans for a remote tele surgery multipurpose robotic
system intended for long distance trauma in battlefield settings. While tele surgery showed impressive performance, the marketable focus has turned away from this goal (George, et al. 2018).

Actual clinical use of robotic surgery began in 1985 with the first surgical robot, an industrial mechanical arm with a control system, PUMA 560, in a stereotaxic operation with brain biopsy guided by computed tomography. In the late 1980s the PROBOT was developed at the Imperial College London, England, and was used to perform transurethral prostate surgery. In the telepresence concept in 1986 the surgeon was wearing a Head Mounted Display and Data Gloves to control the operative instruments remotely. The technique had to be developed because the gloves failed to have sufficient precision in surgery.

The American company Integrated Surgical Systems and the International Business Machines Corporation developed the ROBODOC in 1992, as an orthopaedic image-guided system for use in prosthetic hip replacement. With the system’s pre-surgical 3D planning, exceptional accuracy in component selection, placement, surface preparation and soft tissue management was possible in prosthetic surgery.

Computer Motion, Inc. California, US, was founded with the goal of creating an endoscopic holder. With the initial funding from NASA and DARPA the Automated Endoscopic System for Optimal Positioning (AESOP) was developed in 1992. AESOP was the first robot to receive FDA clearance for use in the operating theatre and used voice-controlled commands to provide hands-free intraoperative manoeuvring. AESOP was adopted in more than 1,000 hospitals and represented the beginning of the global impact of the robotic surgery. The company accelerated the development of the robotic system with HERMES and then in 1996 came ZEUS, the first complete robotic surgery system with the advantage of having the capacity of remote surgery and also the first surgical robot to complete transatlantic surgery. However, this was first used many years later in September 2001; a cholecystectomy was performed from New York City and the patient, a 68-year-old woman, was in Strasbourg, France (Marescaux, et al. 2001).

During the same time period Intuitive Surgical, Inc. California, US, was founded and developed in 1996 a first robotic prototype “Lenny” and in 1997 “Mona”. Remote surgery as with ZEUS was not possible because the Intuitive Surgical robotic system was directly connected to the surgeon’s console by a cable. The first human robotic operation was also a cholecystectomy performed with “Mona” on a 72-year-old woman, March 1997 in Belgium (Himpens, et al. 1998, Cadiere, et al. 1999).

In 1999, a conflict arose between the two competitors Computer motion and Intuitive Surgical about patents and licences and a lawsuit followed. In 2003 the two companies merged and shortly after, the ZEUS robot was phased out of production; however, many of its elements were integrated in later versions of the da Vinci robotic system, initially developed in 1999. The robots used today are refined models of the da Vinci (shown in Figure 4).

Although the robotic system has existed for more than 20 years and seems clinically effective, the majority of published papers are feasibility and safety studies in a retrospective or prospective setting. There is still a lack of high-quality randomised controlled trials in gynaecological oncology surgery and endometrial cancer treatment even if the method seems to be safe to use (Park, et al. 2016). Even oncologic safety and long-term outcomes following
robotic surgery need to be investigated with high-level evidence. In early endometrial cancer one RCT showed that laparoscopic surgery is safe regarding oncologic outcomes such as cancer recurrence and survival rate (Walker, et al. 2012). However in surgery of early cervical cancer there is RCT evidence showing a higher recurrence rate and worse overall survival after using the minimally invasive technique, mostly laparoscopically but also robotically, compared with open surgery (Ramirez, et al. 2018, Printz 2019). Another aspect of robotic surgery is the currently ongoing debate about the benefit of the technique versus the markedly increased costs of acquisition and maintenance of the robot (Kristensen, et al. 2017, Nevis, et al. 2017, Lawrie, et al. 2019).

Figure 4. The robotic surgery system today ©[2020] Intuitive Surgical, Inc.
Health economics and health-related quality of life (HRQoL)

Health economic evaluations, along with clinical outcomes, are important in decision-making and priority-setting regarding the introduction and acceptance of new treatment procedures in relation to resource use. There are several types of economic evaluations (Drummond, et al. 2015). A cost analysis compares only the costs for the different treatments or health care programmes. In a cost-effectiveness analysis both costs and effects or consequences of the treatment are compared within groups, as shown in Figure 5. The cost-utility analysis is a cost-effectiveness analysis with the addition of QALY as an outcome measure. A cost-benefit analysis considers both costs and benefits expressed in monetary units.

A cost-utility or a cost-effectiveness analysis with QALY as an outcome requires the measurement of the HRQoL, which can be done by several modalities, appropriately by questionnaires like the EuroQol Group-five dimensions-three levels form (EQ-5D-3L) investigating general health aspects or by other more disease specific surveys with a linked weighted health index or health profile (Drummond, et al. 2015). A QALY is a measure incorporating mortality (quantity) and morbidity (quality). One QALY is one year in full health (Figure 6). In a cost-utility analysis the health improvement is measured in QALYs gained, and this gain in QALYs is compared with costs.

Figure 5. The cost-effectiveness modalities.
Figure 6. Different conditions with the same QALY (Quality-Adjusted Life Years).

The incremental cost-effectiveness ratio (ICER) in the cost-effectiveness analysis shows the additional cost needed to produce an additional unit of health outcome when treatment (T) is given rather than control (C) (Drummond, et al. 2015).

\[
\text{ICER} = \frac{\text{COST}_T - \text{COST}_C}{\text{QALY}_T - \text{QALY}_C}
\]

For decision rules, a threshold for cost-effectiveness or willingness to pay (WTP) for a QALY needs to be introduced (Drummond, et al. 2015). This threshold can be expressed in monetary units and is usually country-specific and can vary between and within countries over time. The cost-effectiveness plane and WTP are demonstrated in Figure 7.

Figure 7. The cost-effectiveness plane and willingness to pay (WTP)
Recently a systematic review of costing methodology in robotic surgery in gynaecology revealed a lack of high-quality trials reporting on resource use and costs (Korsholm, et al. 2018). To obtain a more comprehensive understanding of the effects and costs, it seemed essential to include and evaluate a cost-effectiveness analysis, with QALY as an outcome measure, in our study about robotic hysterectomy compared with abdominal hysterectomy for treating early endometrial cancer in an ERAS programme. The analysis was also important in order to evaluate whether this treatment method could lead to an improvement in the care of women with early endometrial cancer.
Theory and Hypotheses

In the search for methods that could lead to medical and surgical improvements in the care of women undergoing gynaecological cancer surgery we wanted to focus on tranexamic acid in ovarian cancer surgery because of the positive effects of the drug obtained in multiple benign surgery settings without any reports of increasing bleeding effects. To investigate whether the drug had the same benefit in ovarian cancer surgery, which has risk for excessive bleeding, was appealing. Avoiding a blood transfusion in cancer surgery should be considered as advantageous for both the patient and society.

Many factors influence recovery after surgery. The mode and extent of surgery and the related tissue damage, as well as complications, are thought to affect postoperative recovery. The use of an ERAS programme optimises the perioperative care of the patient and decreases postoperative complications. We wanted to combine ERAS and robotic surgery, as an advanced type of laparoscopic technique, for treatment of early endometrial cancer. We also wanted to determine whether this method could improve the care of women with endometrial cancer considering HRQoL, postoperative recovery, tissue damage and health economic factors compared to the traditional abdominal approach.

Based on the considerations described above the following hypotheses were proposed.

Hypotheses

- A single dose of tranexamic acid given intravenously immediately before the operation for presumed advanced ovarian cancer reduces perioperative blood loss and the need for blood transfusions compared with placebo.

- Women undergoing robotic hysterectomy in an ERAS programme in treatment of low-risk endometrial cancer have a faster recovery as regards HRQoL, fewer postoperative symptoms, and a shorter hospital stay compared with women undergoing abdominal hysterectomy.

- Robotic hysterectomy in an ERAS programme in treatment of low-risk endometrial cancer results in less tissue damage and a reduced inflammatory response compared with abdominal hysterectomy.

- Health economic evaluation will be in favour of robotic hysterectomy compared to abdominal hysterectomy in an ERAS programme in treatment of low-risk endometrial cancer.
Aims

General aim

- To explore medical and surgical treatment methods that can improve the care of women undergoing gynaecological cancer surgery.

Specific aims

- To determine if a single dose of tranexamic acid given intravenously immediately before the operation for presumed advanced ovarian cancer reduces perioperative blood loss and the need for blood transfusions compared with placebo.

- To investigate if postoperative recovery as regards HRQoL and postoperative symptoms differs between women operated with robotic or abdominal hysterectomy in an ERAS programme in treatment of low-risk endometrial cancer.

- To study the dynamics of tissue damage and inflammatory response markers perioperatively and study whether these markers differ between women operated with robotic and abdominal hysterectomy in an ERAS programme in treatment of low-risk endometrial cancer.

- To compare proportional total costs for hospital stay and postoperative recovery between robotic and abdominal hysterectomy in an ERAS programme in treatment of low-risk endometrial cancer and to evaluate cost in relation to health impact through a cost-effectiveness analysis with QALY as an outcome.
Material and Methods

Study design, population and outcomes

The Cyklokapron study

Design
The study was a randomised prospective double-blind placebo-controlled multicentre study comparing the drug tranexamic acid and placebo (a saline solution (0.9% NaCl)), given intravenously immediately before surgery for presumed advanced ovarian cancer. The departments of Obstetrics and Gynaecology at two university and two central hospitals in the south-east and central region of Sweden participated: the University Hospital in Linköping, the University Hospital in Örebro, the Central Hospital in Kalmar, and the Central Hospital Ryhov in Jönköping. One hundred women were included.

A computer generated the randomisation sequences with the web programme SISA (http://home.clara.net/sisa/randmiz.htm), creating blocks of ten with an equal number of allocations (1:1) to tranexamic acid and placebo for each of the four participating centres. The participating centres were assigned slightly different numbers of blocks corresponding to the expected number of eligible patients at the hospital. Each individual assignment from the computer-generated sequences was numbered sequentially and this code number was associated with the allocated treatment in a code list. The randomisation was performed immediately after informed consent was given. The code list with the information on the corresponding allocated treatment was kept in the local hospital pharmacy where the study medication was prepared. Along with information on the weight of the patient and the date of surgery the code number was sent to the local hospital pharmacy after the randomisation was performed.

Population
Women who were admitted to the participating units for presumed (clinically and/or radiologically) or confirmed advanced ovarian cancer and scheduled for explorative laparotomy with the aim of performing radical debulking surgery between March 2008 and May 2012 were asked to participate in the study according to the inclusion and exclusion criteria as presented in Table 1.

After giving informed consent, the included women were allocated to groups receiving either infusion of a single dose of tranexamic acid or placebo intravenously immediately before surgery. The flowchart of the Cyklokapron study is presented in Figure 8.
Table 1. Inclusion and exclusion criteria in the Cyklokapron study.

| Inclusion criteria                                                                                                                                                                                                 |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| • Women ≥ 18 years of age                                                                                              |                                                                                                           |
| • Scheduled for radical debulking explorative laparotomy for presumed advanced ovarian cancer                                                                                                                      |                                                                                                           |
| • ASA ≤ class 3                                                                                                         |                                                                                                           |
| • Speaking Swedish fluently and understanding it equally well                                                        |                                                                                                           |

| Exclusion criteria                                                                                                                                                                                                 |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| • Allergy to tranexamic acid                                                                                                                                        |                                                                                                           |
| • Treatment with anticoagulants within the past month                                                                                                              |                                                                                                           |
| • History or present laboratory signs of bleeding disorders, coagulopathy or thromboembolic events                                                                                                                  |                                                                                                           |
| • History of myocardial infarction within the last year                                                                                                              |                                                                                                           |
| • Present unstable angina or severe coronary disease                                                                                                                 |                                                                                                           |
| • Reduced renal function with plasma creatinine above 250 μmol/l                                                                                                 |                                                                                                           |
| • Severe psychiatric or mental disorder                                                                                                                              |                                                                                                           |

Outcomes
The main outcome measures were perioperative blood loss and RBC transfusion. As secondary outcomes we had the difference in number of blood transfusions given in the respective treatment group, the presence of venous thromboembolic events and postoperative complications until the five-week postoperative visit.
Enrolment

Assessed for eligibility (n=193)

Not meeting inclusion/exclusion criteria, declined to participate or not asked to participate (n=93)

Randomized (n=100)

Allocated to tranexamic acid (n=50)

Allocated to placebo (n=50)

Analysis Intention-to-treat

Underwent surgery (n=50)

Did not receive allocated intervention: Logistical problem with study medication (n=1)

Withdrew consent prior to 5-weeks follow-up, (n=1) (Information about postoperative events after discharge retrieved in patient file)

5-weeks follow-up visit (n=48)

Underwent lower extremity duplex ultrasound examination (n=26)

Analysis Per Protocol

Did not receive allocated intervention: Logistical problems with study medication (n=3) Protocol violation (n=1)

Withdrew consent prior to 5-weeks follow-up, (n=1) (Information about postoperative events after discharge retrieved in patient file)

5-weeks follow-up visit (n=45)

Underwent lower extremity duplex ultrasound examination (n=30)

5-week Follow-Up

Figure 8. Flowchart of participants in the Cyklokapron study.
The Robothyst study

Design
The study was a prospective randomised open controlled single centre trial comparing robot-assisted laparoscopic hysterectomy and abdominal hysterectomy in women undergoing surgery for low-risk early stage endometrial cancer. The department of Obstetrics and Gynaecology at the University Hospital in Linköping, Sweden recruited the patients, and a total of 50 women were included. The web programme SISA (http://home.clara.net/sisa/randmiz.htm) generated a balanced randomisation with sequences into blocks of ten with an allocation ratio 1:1 to robotic or abdominal hysterectomy. The woman was informed about the allocated method after signing an informed consent form.

Population
Women with low-risk early stage endometrial cancer scheduled for radical surgery at the University Hospital in Linköping between February 2012 and May 2016 were asked to participate in the study according to the inclusion and exclusion criteria shown in Table 2.

Table 2. Inclusion and exclusion criteria in the Robothyst study.

| Inclusion criteria                                                                 |
|----------------------------------------------------------------------------------|
| • Women ≥ 18 years of age                                                       |
| • Scheduled for surgical treatment of FIGO stage I, low-risk endometrial cancer (endometroid adenocarcinoma FIGO grade 1 and 2) with planned hysterectomy with bilateral salpingo-oophorectomy and peritoneal washings for cytology |
| • WHO performance status ≤ 2 (unable to work, active more than 50% of the day)   |
| • Speaking Swedish fluently and understanding it equally well                    |

| Exclusion criteria                                                               |
|----------------------------------------------------------------------------------|
| • Laparoscopic approach not considered suitable                                   |
| • A planned midline incision                                                     |
| • More extensive surgery than hysterectomy and bilateral salpingo-oophorectomy planned |
| • Any condition excluding the woman from having intrathecal morphine analgesia   |
| • Immunosuppressive medication                                                   |
| • Physically disabled                                                           |
| • Severe psychiatric or mental disorder                                         |

The flowchart of the Robothyst study is depicted in Figure 9.
Figure 9. Flowchart of participants in the Robothyst study.
Outcomes
The main outcome measure was HRQoL.
Secondary outcomes were postoperative symptoms, analgesic consumption, length of hospital stay, postoperative complications, markers of tissue damage and inflammation, health economics including direct and indirect costs, QALY, and cost per QALY gained.

Methods

The Cyklokapron study

Perioperative, surgical procedure and follow up
All participants had a routine preoperative evaluation and standard preadmission testing including a CT scan. The patients received a single dose of prophylactic antibiotic preoperatively. Thrombosis prophylaxis was given with low molecular heparin (tinzaparin 4,500 anti-Xa IE or dalteparin 5,000 IE) once daily for 28 days postoperatively. Surgery was performed under standard general anaesthesia and an epidural analgesic was allowed perioperatively.
The study medication containing either tranexamic acid, or saline as a placebo (0.9% NaCl) was prepared on the day of surgery by the local hospital pharmacy. The volume of tranexamic acid (15 mg/kg body weight, 100 mg/ml Cyklokapron®, Pfizer AB, Sollentuna, Sweden) or the same volume of placebo (0.9% NaCl) was added to a 100 ml saline solution plastic bag. All hospital staff and patients were blinded to the treatment.
The patients received the study medication before the start of the operation as an intravenous infusion given over a period of 15-20 minutes. The infusion was started immediately after the general anaesthesia had been established. The laparotomy was conducted through a midline incision. The primary intention of the surgery was to completely remove the tumour. In the event that this was considered impossible by the surgeon, the secondary goal was to obtain debulking of the tumour to minimal residual disease less than 1 cm. If even this was considered impossible the surgical procedure was limited to taking gross samples from the ovaries and tumour masses to secure a histopathological diagnosis. All operations were performed by experienced gynaecological oncology surgeons. Perioperative bleeding was managed according to clinical practice and a blood transfusion was usually given when the haemoglobin level measured during the surgery or postoperatively was below 90 g/l.
Administration of a supplemental single dose of 1,000 mg tranexamic acid and/or a single dose of desmopressin (0.3 μg/kg body weight) was allowed if the surgeon observed an unacceptable level of bleeding during surgery. Drainage was allowed but not encouraged. A postoperative blood transfusion was given depending on the patient’s clinical well-being and haemoglobin level. Allogenic leuco-depleted packed RBC concentrate was given in 250 ml units. Plasma transfusions were usually given in the case of heavy bleeding in a proportion of one unit RBC to one unit of plasma.
At the five-week postoperative visit, the patient was seen by the research nurse and interviewed about postoperative complications, in particular wound complications and thromboembolic events. Concurrently, patients were optionally referred for a lower extremity
duplex ultrasound in order to look for venous thrombosis, regardless of symptoms. The ultrasound examinations were performed at the Department of Clinical Physiology using an ACUSON S2000™ ultrasound system (Siemens Medical Solutions USA, Inc.), (7-9 MHz-transducer). Both legs were investigated by compression ultrasound using the technique described by Schellong et al. (Schellong, et al. 2007).

The extent of the surgery was operationalised into “extensive debulking” and “diagnostic”. Extensive debulking was defined as surgery comprising hysterectomy, bilateral salpingo-oophorectomy, resection of the omentum majus and/or resection of the liver, bowel, peritoneum, appendectomy and pelvic and para-aortic lymphadenectomy. The surgery was classified as “diagnostic” when the surgeon found it impossible to reduce the disease to at least minimal residual disease and only samples were obtained for histopathological diagnosis.

Estimation and calculation of blood loss

The haemoglobin level was assessed preoperatively (Hbpre, g/l) and on the fifth postoperative day or on the day of discharge if the patient was discharged earlier (Hbpost, g/l).

Various dimensions of blood loss were assessed:

1) Estimated perioperative blood loss

Perioperative blood loss volume was estimated visually by the nurse anaesthetist as the blood remaining in sponges and drapes and the volume in suction bottles during surgery.

2) External blood loss (i.e. perioperative blood loss + blood loss in drains)

Postoperative blood loss in drains was determined by measurement of the fluid volume and drainage haemoglobin with the HemoCue® apparatus (HemoCue AB, Ängelholm, Sweden). The blood loss in drains was adjusted for the patients’ Hbpre.

3) Total blood loss

Estimation of total blood loss was based on the estimation of the Hb balance method (Brecher, et al. 1997) with the assumption that the body blood volume was normalised on the fifth postoperative day.

The predicted blood volume (PBV, l) was calculated according to the method described by Nadler et al. (Nadler, et al. 1962), using body weight (W; kg) and height (H; m):

\[
PBV = 0.3561 \times H^3 + 0.03308 \times W + 0.1833
\]

The extravasation of haemoglobin (Hbloss, g) was calculated according to the formula:

\[
Hbloss = (Hbpre - Hbpost) \times PBV + Hbt.
\]

Hbt is the total amount of allogenic transfused haemoglobin (g). One unit of erythrocytes contained 56 g of haemoglobin (SD = 5.4 g) (personal communication with the Department of Transfusion Medicine, University Hospital, Linköping, Sweden).

Total blood loss was related to the patient’s Hbpre value.

Total blood loss (ml) = 1,000 × Hbloss / Hbpre.
4) **Occult (or hidden) blood loss**

Occult blood loss (ml) = Total blood loss – (Perioperative blood loss + blood loss in drains).

If a reoperation was performed within the first five days after surgery the estimated bleeding volume at the re-operation was also included in the occult blood loss.

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**The Robothyst study**

Perioperative, surgical procedures and follow-up

The participants had a routine preoperative evaluation (www.SFOG.se) and received identical perioperative advice and information about the care according to the ERAS programme, including the expected length of hospital stay, the postoperative period with treatment on the ward, and the criteria for discharge. Preoperatively the women received routine thrombosis prophylaxis with low molecular weight heparin (tinzaparin 4,500 anti-Xa IE) once daily for 28 days postoperatively, and a single dose of prophylactic antibiotic. Prior to the general anaesthesia the women received an intrathecal combination of bupivacaine 20 mg and morphine 0.2 mg (women older than 70 years received bupivacaine 15 mg and morphine 0.1 mg). The general anaesthesia was standardised: induction with fentanyl and propofol, intubation facilitated with rocuronium and maintenance with sevoflurane. To prevent hypothermia, insufflation of heated CO₂ was used in the robotic surgery. In the laparotomy group a hot air blanket was applied to the upper part of the body. A local anaesthetic was injected in the area of the skin incision in both groups.

The abdominal hysterectomy was conducted through a transverse lower abdominal skin incision with the woman in the supine position. The robotic hysterectomy was performed with four robotic ports and three robotic arms using the *da Vinci®*, Surgery System. In robotic hysterectomy the women were placed in a 30-degree Trendelenburg position with the legs in lithotomy stirrups. Basically, the surgery was performed according to the technique applied in minimally invasive surgery with the use of a bipolar vessel sealing device in both treatment groups.

All operations were performed by gynaecological oncology surgeons; one skilled robotic surgeon operated robotically and six surgeons performed the abdominal surgery. Time point of arrival at the operating theatre, duration of anaesthesia and surgery time was recorded, as time in the post anaesthesia care unit (PACU).

Postoperatively the women received basic analgesics comprising oral paracetamol 1,330 mg (665 mg x 2) and diclofenac 50 mg three times daily as long as the patient considered it necessary. Rescue IV morphine, ketobemidon 0.5-1 mg, or oral oxycodone 5 mg was given if needed.

To quantify the amount of non-opioid analgesics given, the WHO-defined daily dose (DDD) methodology was used (www.whocc.no). All opioids given, independent of administration route and including the intrathecal morphine, were registered and converted into an equivalent intravenous morphine dose (Caraceni, et al. 2012).
The standardised criteria for discharge were that the woman was ambulatory, could tolerate a normal diet, had sufficient pain relief with oral analgesics (≤4 on a numeric rating scale from 0 to 10), had voided spontaneously with less than 150 ml residual urine and showed no signs of mechanical bowel obstruction. These criteria were checked twice daily. The time of arrival at the operating theatre and the time of discharge from the ward were registered. Consequently, the actual length of hospital stay as well as the time to when the discharge criteria were met could be calculated.

Perioperative complications during the hospital stay were registered. After discharge, the woman was requested to complete a diary for six weeks recording analgesic consumption and recovery of bowel function. The woman also wrote down the kind and extent of postoperative support in the household or informal care, if any, performed by a relative, friend or neighbour. The time spent receiving informal care, was registered by the patient in hours per week and subsequently added up for all weeks.

Sick leave was provided as long as the women needed it, though initially it was granted for four weeks with the possibility to return to work earlier if this was appropriate. Besides the physical recovery after the operation also existential, psychological factors must be considered before a return to ordinary work is possible. The duration of sick leave was defined as the time from the day of surgery until the day of resuming work at the same intensity as before the operation.

The research nurse called the patient the day after discharge and then once weekly until the six-week outpatient visit to ask about complications and to remind the participant to complete the questionnaires.

A summary of the ERAS programme is shown in Table 3.
Table 3. The ERAS protocol with standardised regimes.

| Preoperative Information | Repeated information was given concerning perioperative care, management of pain, nausea, vomiting, early postoperative mobilisation, enteral nutrition, and discharge criteria. |
|--------------------------|---------------------------------------------------------------------------------------------------------------------------------|
| Premedication            | Paracetamol 3 x 665 mg orally was given one hour before surgery. Clear fluids orally until two hours before surgery. Acupressure wrist bands applied and maintained through hospital stay. |
| Intraoperative Parenteral fluids | 250 ml colloid fluid (venofundin) during application of spinal anaesthesia. Other fluid therapy as prescribed by the anaesthesiologist. |
| Spinal anaesthesia       | < 70 years intrathecal bupivacaine 20 mg and morphine 0.2 mg ≥ 70 years intrathecal bupivacaine 15 mg + morphine 0.1 mg. |
| General anaesthesia      | Induction fentanyl and propofol, intubation facilitated with rocuronium. Maintenance with sevoflurane and ventilation with air/oxygen. Further rocuronium and fentanyl if necessary. |
| Local anaesthesia Prevention | Antibiotic and antithrombotic prophylaxes were administered according to the routine of the department. |
| Bladder catheter         | A transurethral catheter was inserted before start of surgery and removed the next morning. |
| Postoperative Post anaesthesia care unit (PACU) | Pain management orally with paracetamol 665 mg 2 x 3 and diclofenac 50 mg 1 x 3. Additional pain management with morphine IV if VAS (visual analogue scale) score > 3. Liquid permitted. Mobilisation encouraged. Rescue antiemetic treatment if requested with droperidol and/or 5-HT3 receptor antagonist. Discharge to the gynaecological ward when vital signs were stable. Monitoring of haemodynamic and respiratory stability, sedation, pain, nausea and pruritus once every hour during the first 12 hours postoperatively, then once every third hour for another 12 hours. Pain management continued, orally 1,330 mg paracetamol and 50 mg diclofenac x 3. Additional pain relief if VAS score >3. Avoidance of opioids if possible. Rescue antiemetic treatment as in PACU. Early nutrition. Active mobilisation. |
| Gynaecological ward      | Woman is mobile. Tolerates a normal diet. Sufficient pain relief with oral analgesic (VAS < 4). Voiding with residual urine ≤ 150 ml. No signs of bowel obstruction. |
| Discharge criteria        | Pain management continued with 1,330 mg paracetamol and 50 mg diclofenac x 3. If NSAID contraindicated tramadol 50 mg x 4. A package of six tablets of oxycodone (10 mg x 2 daily) if necessary. Duration of analgesic treatment decided by the woman. |
| After discharge from hospital | Pain management continued with 1,330 mg paracetamol and 50 mg diclofenac x 3. If NSAID contraindicated tramadol 50 mg x 4. A package of six tablets of oxycodone (10 mg x 2 daily) if necessary. Duration of analgesic treatment decided by the woman. |
Measurement of HRQoL (EQ-5D-3L and SF-36)

Two validated generic forms, the EuroQol Group five-dimensions three-level form (EQ-5D-3L) (EuroQol-Group 1990) (Appendix 2) and the Short-Form Health Survey (SF-36) (Sullivan, et al. 1995), were used to assess the HRQoL.

1. **EQ-5D-3L**

The form comprises five dimensions of health (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). Each dimension has three levels (no problems, some/moderate problems or major problems). A unique EQ-5D-3L health state as a utility measure is defined by combining one level from each of the five dimensions, thus defining $3^5 = 243$ possible health states or health profiles, to which have been added ‘unconscious’ and ‘dead’ for a total of 245 possible health profiles. To each defined health status in the classification system a preference score or a weight (quality-of-life weight) has been determined. The preferences for the scoring function were measured on a utility scale with the Time to Trade Off technique (Dolan and Gudex 1995).

The weighted health state index ranges from -0.594 to 1. Zero indicates the state of death and 1 indicates good health. A figure less than 0 indicates a state worse than death which cannot be translated into a clinical categorisation but can be used for the purpose of tracing and analysing changes in health state over time.

In the Robothyst trial the EQ-5D-3L form was completed preoperatively after the randomisation, from the day of surgery daily during the first eight days after the operation, and then once weekly until the six-week postoperative visit.

2. **SF-36**

The SF-36 is widely used for assessments of HRQoL and is a practical alternative for measures for a longer period. This generic, descriptive, multipurpose, Short-Form Health Survey consists of 36 questions yielding an eight-scale health profile of scores. Sum scores are calculated for each component: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health. Additionally, the physical component summary score (PCS) and the mental component summary score are calculated separately. All scores are on a scale from 0 to 100. A higher score means a better HRQoL.

In the Robothyst trial the Short Form-36 was completed twice, preoperatively and six weeks postoperatively.

Measurement of postoperative symptoms (SPSQ)

The Swedish Postoperative Symptom Questionnaire (SPSQ), a validated form including ratings of eight symptoms commonly reported after surgery, was used to assess the postoperative symptoms (Alkaissi, et al. 2004, Wodlin, et al. 2011a). The SPSQ was developed for gynaecological surgery patients in order to evaluate postoperative symptoms based on the patient’s own experience of recovery in three different aspects: currently, on average, and at peak during the day, and has both open- and closed-ended questions.

The evaluated symptoms were nausea, retching, headache, abdominal pain, tiredness, drowsiness, blurred vision and itching. The answers were rated on a four-point scale from “none”, one point, to “yes, a lot” which gave four points. To estimate overall discomfort a
postoperative symptom sum score of the eight symptoms was calculated (minimum sum score 8, maximum 32). The higher the sum score, the more discomfort the patient experienced. The participant was also asked to report the pain intensity in the surgical area at peak and on average on the particular day, rated on a seven-point Likert-type scale. Other annoying postoperative symptoms (gastro-intestinal, urinary tract, musculoskeletal, wound-related and sleep quality) were also registered and their intensity reported.

In the Robothyst study the SPSQ was filled out daily at the same time every day, starting the evening after surgery (Day 0) and continuing for the first seven days postoperatively. Then the SPSQ was completed once weekly until the six-week postoperative visit.

Measurement of anxiety and depression (HADS), and pain sensitivity (PSQ)
Anxiety, depression and pain sensitivity are factors that may influence postoperative recovery. In order to assess the balance of these conditions between the groups the participants completed the Hospital Anxiety and Depression Scale form (HADS) and the Pain Sensitivity Questionnaire (PSQ) preoperatively (Bjelland, et al. 2002, Ruscheweyh, et al. 2009).

1. **HADS**
   A frequently used self-rating scale developed to assess psychological distress in non-psychiatric patients. The questionnaire consists of 14 items, seven items for the anxiety subscale (HADS Anxiety) and seven for the depression subscale (HADS Depression).
   HADS Anxiety focuses mainly on symptoms of generalised anxiety disorder and HADS Depression is focused on anhedonia (loss of interest and pleasure), the main symptom of depression. Each item is scored on a response-scale with four alternatives ranging between 0 and 3. After adjusting for six items that are reversed scored, all responses are summed to obtain the two subscales.
   Recommended cut-off scores are 8-10 for doubtful cases and ≥ 11 for definite cases (Zigmond and Snaith 1983).

2. **PSQ**
   The questionnaire is based on a pain intensity rating of imagined painful situations occurring in daily life. It consists of 17 items, describing different daily life situations with a scoring from 0 (not painful) to 10 (worst pain imaginable) on a numeric rating scale. Fourteen items are directed towards situations that are considered painful by the majority of healthy subjects and three items are directed towards non-painful situations as perceived by most people. These three items are meant to serve as a non-painful sensory reference for the participants and are not used in the final score. The painful items represent diverse types of pain such as hot, cold, sharp and blunt, and different body sites such as the head, upper and lower extremity. The PSQ can be summed in a total score, a PSQ minor and PSQ moderate score. We used this survey to assess whether there was a difference in baseline pain sensitivity between the groups, and not with the intention of classifying any pain pathology.
Measurement of tissue damage and inflammation
We selected a panel of markers that previously has been shown to reflect acute inflammation and response to tissue trauma caused by surgery and stress (Brochner and Toft 2009, Lombao et al. 2014, Pilka, et al. 2016, Bianchi, et al. 2017). The selected inflammatory and immunological markers were hsCRP, white blood cells (WBC), thrombocytes, IL-6, the tissue damage markers CK, and HMGB1, and the stress hormone cortisol.

- Collection and analysis of blood samples
Markers of inflammatory response and tissue damage were evaluated in peripheral venous blood. Blood samples were collected on seven occasions from all women:

- Time 1 = one week before surgery
- Time 2 = on the day of surgery before the operation
- Time 3 = two hours postoperatively
- Time 4 = 24 hours postoperatively
- Time 5 = 48 hours postoperatively
- Time 6 = one week after surgery
- Time 7 = six weeks after surgery

The samples were centrifuged within one hour after collection and the aliquots frozen at -70 degrees Celsius. Analyses of the samples were carried out on one occasion, except for cell counting, which was performed immediately after the blood sample collection.

- Methods of laboratory analyses
The hsCRP and cortisol levels were measured using a Cobas e 602 analyser as part of a Cobas 8000 modular analysis series (Roche Diagnostics, Germany) using a latex particle-enhanced immunoturbidimetric assay (‘Cardiac C-Reactive Protein (Latex) High Sensitive’ reagent kit) and Cortisol II reagents (Roche Diagnostics, Germany), respectively.

The WBC and thrombocytes were analysed using a CellDyn Sapphire Hematology Analyser (Abbott Laboratories, IL, USA).

IL-6 was measured with MILLIPLEX® MAP Kit, Human Cytokine/Chemokine Magnetic Bead Panel (Millipore Corporation, Billerica, MA, USA) on the LumineX®200™ (Invitrogen, Merelbeke, Belgium) instrument according to the manufacturer’s instructions, except that one extra standard point was added to the standard curve by one additional serial dilution. The lowest standard point was 1.6 pg/mL, and values below were assigned half of this value. Data collection was conducted using the xPONENT 3.1TM software (LumineX Corporation, Austin, TX, USA) and data analysis was performed using the MasterPlex 2010 2.0 software (MiraiBio Group, Hitachi Solutions America, Ltd., San Francisco, CA, USA).

CK was measured with a Cobas e 701 analyser as part of the Cobas 8000 modular analysis series (Roche Diagnostics, Germany) using creatine kinase reagents from Roche.

HMGB1 was measured by HMGB1 Elisa (IBL International GMBH, Hamburg, Germany) according to the manufacturer’s instructions. The lower limit of detection was 0.1 ng/mL, and levels below (in 5% of the samples) were assigned a value of 0.05 ng/mL.
Cost-effectiveness analysis with QALY

- Direct costs (Hospital costs)

Relevant direct costs related to hospital stay and follow-up six weeks postoperatively were calculated for the robotic and abdominal hysterectomy group using costs from the year 2018. The costs were calculated in Swedish Crowns (SEK). For other currencies we referred to the average exchange rate in 2018 established by the Swedish National Bank per December 31; 1 US Dollar = 8.6921 SEK and 1 EURO = 10.2567 SEK.

Estimation of cost-generating factors comprised costs related to the operation including surgery time, time in the operating theatre with personnel, procedure and material costs including investment, maintenance and depreciation, and costs associated with hospital care not only during hospitalisation but also due to unplanned readmissions after discharge from the ward.

The hospital internal fees, a fixed “once-and-for-all cost” in three categories for the operation, based on the calculated average real cost of the surgery depending on the extent of the intervention, and the “per minute charge” for the surgery, a variable cost depending on the duration of surgery, were used from the cost accounting records from the University Hospital, Linköping, for the year 2018. The variable cost for total time in the operating theatre, excluding the surgery, included mean salaries from the year 2018 for the nurse anaesthetist, the operating theatre nurse and the assistant nurse working at that time (www.scb.se). The salary for the anaesthesiologist was not included here because the procedure of spinal analgesia with intrathecal morphine (25 minutes) and general anaesthesia (15 min) was the same in each group and thereby only proportionately increased costs in the groups. The cost for the anaesthesiologist during the operation was included in the “per minute charge” for the operation. The costs for the nurse anaesthetist, operation room nurse and assistant nurse were calculated as a mean of the yearly salary in Sweden multiplied by 1.43 to include the social fees regulated by law (Hjalte, et al. 2018). A full time employment covers approximately 200 days annually and the time spent in the operating theatre is approximately eight hours per day. With a mean annual cost of SEK 677,820 for the nurse anaesthetist, SEK 689,832 for the operating nurse and SEK 490,776 for the assistant nurse this yields a cost per minute of SEK 7.1, SEK 7.2 SEK and SEK 5.1, respectively. The cost for the surgeons was calculated similarly, and two surgeons yield a combined cost per minute of SEK 46.

The procedure cost for the robotic hysterectomy covered the purchase price of the robot, the da Vinci® Si System with camera and optics (SEK 14,022,750 in 2007) with a depreciation time of eight years, and the yearly maintenance fee (SEK 1,307,600 in 2007) taking into account that the first year was free of charge. With an annual caseload of 300 robotic operations, on average six procedures a week over 50 weeks, the procedure price tag was SEK 9,657 per robotic operation. Surgical equipment like the container with surgical robotic instruments (Maryland forceps, needle driver and monopolar scissors) was specified, taking into account the lifetime of the instruments, which is limited to ten separate procedures, and the lifetime of the container of ten years. Costs for sterilisation of instruments, draping and extra material used with the operation were also calculated. The procedure cost for the open hysterectomy consisted of the reusable surgical instruments including the bipolar vessel...
sealing device (Ligasure®, Medtronic, Minneapolis, MN, USA). We assumed the lifetime of the abdominal hysterectomy instruments container to be 10 years.

The length of hospital stay in the gynaecological ward was determined as the time in hours from arrival at the operating theatre to discharge from the ward. Costs for the hospital stay in the ward were derived from cost accounting records and amounted to SEK 9,240 per 24 hours in 2018. This cost comprised salaries for all types of personnel involved, laboratory analyses, the use of pharmaceuticals and the costs for the facilities, heating and cleaning. The number of unplanned readmissions after discharge from the ward was registered in both groups. The unit price of SEK 3,005 was set for an outpatient visit to the doctor and SEK 2,196 for a visit to the nurse.

- **Indirect costs (Societal costs)**

  Duration of sick leave was defined as the time from the day of surgery to the day when the women could return to work at the same intensity as preoperatively. Most participants in the study were already retired but a small proportion was still working fulltime or part-time. The women received sick leave as long as they were considered to need it. Costs for productivity loss due to sick leave were estimated by the human capital approach, based on the average annual income for women aged 20-64 years in Sweden in 2018, which was SEK 391,200 (www.scb.se), multiplied by 1.43 including social benefits (Hjalte, et al. 2018). The annual income was divided by 365 to get the cost of productivity loss per day, SEK 1,533.

  The weekly reported informal care, given by a relative, friend or neighbour to the women after discharge from the gynaecological ward, was summed in hours for all weeks. Based on the human capital approach, the informal care was valued by its opportunity cost. The opportunity cost of leisure time was valued based on a study by Johannesson et al. with one hour of leisure time valued as 35% of the gross wage rate (Johannesson, et al. 1991). According to the general mean income in Sweden for the working population in 2018, which was SEK 415,200 (www.scb.se), and taking into account the social fees, the informal care costs were determined to be approximately SEK 71 per hour (Hjalte, et al. 2018).

  The costs in SEK for all items are shown in Table 4.
Table 4. Mean cost (in SEK) per item and operation with a yearly caseload of 300 and 500 operations

| Cost per item (SEK)                                      | Robotic hysterectomy | Abdominal hysterectomy |
|---------------------------------------------------------|-----------------------|-------------------------|
|                                                         | De facto 300          | Optimal 500             | De facto 300 | Optimal 500 |
| Fixed cost for the operation (preparation and closing of theatre, basic equipment) | 5,818                 | 5,818                   | 5,818       | 5,818       |
| Costs for two surgeons (per minute)                     | 46                    | 46                      | 46           | 46           |
| Variable cost for staff excluding surgeons in operating theatre during time of surgery (per minute) | 93                    | 93                      | 93           | 93           |
| Variable cost for nursing staff in operating theatre, excluding time of surgery (per minute) | 19                    | 19                      | 19           | 19           |
| Robotic equipment (including camera and optics; purchase and maintenance) | 9,657                 | 5,794                   | -            | -            |
| Surgical instruments and two instrument containers for robotic surgery | 7,927                 | 7,924                   | -            | -            |
| Surgical instruments and instrument container for laparotomy (including disposable Ligasure®) | -                     | -                       | 2,018        | 2,011        |
| Extra equipment and material                           | 4,000                 | 4,000                   | 2,315        | 2,315        |
| Draping                                                 | 632                   | 632                     | 562          | 562          |
| Sterilisation of instruments                           | 2,521                 | 2,521                   | 615          | 615          |
| Fixed cost for time in post anaesthesia care unit       | 2,399                 | 2,399                   | 2,399        | 2,399        |
| Hospital care in the gynaecological ward (per hour)     | 385                   | 385                     | 385          | 385          |
| Costs of re-admission for 24 hours                      | 9,240                 | 9,240                   | 9,240        | 9,240        |
| Outpatient visit to physician (per visit)               | 3,005                 | 3,005                   | 3,005        | 3,005        |
| Outpatient visit to nurse (per visit)                   | 2,196                 | 2,196                   | 2,196        | 2,196        |
| Costs for sick leave (per day)                          | 1,533                 | 1,533                   | 1,533        | 1,533        |
| Costs for informal care (per hour)                      | 71                    | 71                      | 71           | 71           |

Round figures are used for the convenience of the reader.
Exchange rate per December 31, 2018: US $ 100 = SEK 869.21; € 100 = SEK 1,025.67
Assessment of quality-adjusted life year (QALY)

In order to calculate the QALYs we used the difference in the EQ-5D-3L health state index between the robotic and the abdominal hysterectomy group. For the first eight days the measured EQ-5D-3L index was obtained for each day. For the second to the sixth week after surgery the EQ-5D-3L index was obtained on days 14, 21, 28, 35 and 42. The missing EQ-5D-3L index on the intermediate days in these weeks were replaced by the average of the value for the index on the day of measurement (i.e. on days 14, 21, 28, 35 and 42) and the value the week before (i.e. on days 7, 14, 21, 28 and 35). Consequently, the QALY weights for the robotic and abdominal groups were calculated as the sum of the EQ-5D-3L index in the group for the 43 days divided by 43 days (37.59/43=0.87 for the robotic and 31.12/43=0.72 for the abdominal group). To obtain the QALY gained per person the QALY weights were multiplied by 43 (days)/365 (days) per year =0.12. The calculation was based on the assumption that no further improvement in EQ-5D-3L was obtained after this period of 42 days. Each woman in the robotic group gained 0.87-0.72 = 0.15 x 0.12 = 0.018 QALYs compared with the abdominal group.

Statistics

The Cyklokapron study

Sample size calculation

Sample size estimation was based on the primary outcome of perioperative blood loss, and for the secondary outcome measure sample size estimation was based on the proportion blood transfusions.

\[
N = n_1 + n_2 \\
n_1 = n_2 = 2 \times (\text{PI} \times \text{SD}/d)^2
\]

N = sample size of the study group
n = number of patients
PI = power index, index for power and \(\alpha\) values (level of significance)
SD = standard deviation dependent variable
d = the smallest clinically interesting difference in the dependent variable

For 80% power and \(\alpha = 5\%)\ is \text{PI} 2.8

The SD for blood loss in woman with advanced ovarian cancer undergoing radical debulking surgery from 2000 until 2005 at the department of Obstetrics and Gynaecology, University Hospital in Linköping, was 757 ml. Those receiving blood transfusions had a mean value of blood loss of 1,336 ml and those without transfusions had bleeding of 371 ml (d = 965 ml). It seemed unrealistic to reduce bleeding by 1,000 ml. A reduction of bleeding by 500 ml was considered reasonable.

\[
n_1 = n_2 = 2 \times (2.8 \times 757/500)^2 = 36 \text{ in both study groups, giving a total of 72 patients.}
\]

With a drop-out of 25%, the sample size was estimated to be 90 women.
\[ N = n_1 + n_2, \]
\[ n_1 = n_2 = 2 \times (\pi^2 \times (p_1 \times (1-p_1) + p_2 \times (1-p_2))) / \delta^2 \]

\( p \) = proportion of women requiring blood transfusion
\( \delta \) = difference in proportions

In the sample above, 37\% of the patients with advanced ovarian cancer undergoing radical surgery received a blood transfusion. It seemed reasonable to expect a need for transfusion in the tranexamic acid group of 10\%.

\[ n_1 = n_2 = 2 \times (2.8^2 \times (0.37 \times (1-0.37) + 0.10 \times (1-0.10))) / (0.37 - 0.10)^2 = 35 \]

in both study groups, giving a total of 70 patients.

Including a drop-out of 25\% the sample size was estimated to be 88 women.

A sample size of 100 patients was necessary to detect with an 80\% probability a significant difference in blood loss of 500 ml or a reduction of blood transfusion requirement from 37\% to 10\%, on a 5\% significance level.

Descriptive statistics
Clinical data are expressed as median and range for continuous variables, or number and percentage for categorical or nominal data. Initially the distribution of the data was analysed and since all variables were not normally distributed, continuous data were analysed by means of Mann-Whitney U-test. Pearson Chi-square test and Fishers’ exact test were used for categorical data as appropriate. The analyses were performed with two-sided tests.

Analyses of outcomes
Based on theoretical and clinical considerations we found it reasonable to use one-sided testing for analysing the outcome measures of blood loss volume and transfusion rate since the use of tranexamic acid compared with placebo in clinical trials has consistently been shown to result in lower blood loss and transfusion rates. The outcome measures of blood loss and transfusion rates were compared by means of univariate analyses models; Mann-Whitney U-test was used for continuous data and Pearson Chi-square and Fishers’ exact test were used to analyse categorical data, when appropriate. Multiple logistic regression models adjusted for confounding factors were used for comparing transfusion rates and the results are presented as odds ratio (OR) with an upper 95\% confidence interval (CI) limit. Complications were likewise analysed by means of multiple logistic regression models but with two-sided testing. All analyses were carried out according to the principle “intention-to-treat” (comparison of treatment groups that includes all women as originally allocated after randomisation, and analysed in the group to which they were randomised) and “per protocol” (comparison of treatment groups that included only those who completed the treatment, originally allocated and analysed in the group with the same treatment). The level of significance was set at 5\%.
The Robothyst study

Sample size calculation
Sample size estimation was based on the primary outcome measure, the EQ-5D health index and the secondary outcome measure, the inflammatory marker CRP.

\[
N = n_1 + n_2
\]

\[
n_1 = n_2 = 2 \times (PI \times SD/d)^2
\]

- \(N\) = sample size of the study group
- \(n\) = number of patients
- \(PI\) = power index, index for power and \(\alpha\) values (level of significance)
- \(SD\) = standard deviation dependent variable
- \(d\) = the smallest clinically interesting difference

For 90% power and \(\alpha = 5\%\) is \(PI = 3.2\)

Given the SD of the EQ-5D index (0.2) obtained from data previously published by our institution (Wodlin, et al. 2011b), and based on the assumption that the EQ-5D health index differed by at least 0.2 units between the two groups, we found that with \(\alpha = 0.05\) and \(1 - \beta = 0.90\),

\[
n_1 = n_2 = 2 \times (3.2 \times 0.2/0.2)^2 = 21\]

in both study groups, giving a total of 42 patients. Including a drop-out of 10%, the sample size was estimated to be 50 women.

Based on the assumptions from earlier trials comparing laparoscopic with abdominal hysterectomy, which showed a difference in CRP between the groups of about 30 mg/ml and a standard deviation of 16 mg/ml (Harkki-Siren, et al. 2000, Demir, et al. 2008), we found that with \(\alpha = 0.05\) and \(1 - \beta = 0.90\),

\[
n_1 = n_2 = 2 \times (3.2 \times 16/30)^2 = 6\]

in both study groups, giving a total of 12 patients. Including a drop-out of 10%, the sample size was estimated to be 14 women.

Descriptive statistics
Clinical and demographic data are presented as median and range for continuous variables, or number and per cent for categorical or nominal data. To compare descriptive and clinical data between the two groups in univariate analyses student’s T-test and Mann-Whitney U-test were used for continuous data and Pearson Chi-square and Fishers’ exact test were used to analyse categorical data. The analyses were performed with two-sided tests.

Analyses of outcomes
A repeated measures analysis of variance models, ANOVA, was applied to analyse continuous data measured on more than two occasions. Since perioperative complications may influence recovery, the outcomes were adjusted for perioperative complications occurring before and after discharge. Consequently, it was necessary to divide the timing into two periods in the repeated measures ANOVA models; the first period from day 0 (day of surgery) until day 4 when all women had been discharged, and the second period from day 5
until day 42. Kaplan-Meier survival analysis and the Cox proportional-hazard model were used to evaluate the occurrence of complications.

To ensure that the assumptions of the repeated measures ANOVA were met, assessment of normal distribution of tissue damage and inflammatory markers was performed using normal probability (Q-Q) plots. The homogeneity of variance was assessed using the Mauchly sphericity test. If the sphericity was violated and epsilon <0.75, adjustments of the within subjects factor were made with the Greenhouse-Geisser correction method; if epsilon ≥0.75 the Huynh-Feldt method was applied. Post hoc tests for between groups effects were conducted using the Tukey honestly significant difference test to reveal the significance between the groups on the individual occasions of sampling. As the IL-6 and HMGB1 were not normally distributed, logarithmic transformation of these variables was used.

For all outcomes the significance level was set at p < 0.05 in two-tailed tests. All analyses were carried out according to intention-to-treat principles.

The Software STATISTICA 64 version 12 (StatSoft Inc. 2,300 East 14th St. Tulsa, OK 74104 USA), version 13.2 (Dell Software, 5 Polaris Way, Aliso Viejo, CA 92656, USA) and the software TIBCO Statistica™, version 13.5 (TIBCO Software Inc, Palo Alto, CA 94303, USA) were used to carry out the statistical analyses.

Handling of missing data

When using repeated measures ANOVA, data for every occasion is required and missing answers have to be considered and compensated for in the analysis.

If a separate answer, value or cell was missing, the value was replaced by the mean value of the score for the respective study group on that occasion, the so-called mean imputation method.

If several answers with a calculated sum score were missing, the missing cell was substituted by the truncated mean value of the other items in the specific subscale for the individual participant.

If all cells in a subscale were missing or in the case of a completely missing questionnaire, each cell was substituted by the truncated mean value of the cell for the group on that time of measurement.

Missing cells for the EQ-5D on all occasions made up 1.5 % and no questionnaires were missing. Unfortunately six SF-36 questionnaires were missing postoperatively for unknown reasons, giving missing values on both occasions of 7.8 %. Overall missing blood samples inclusive hsCRP, IL-6, CK, HMGB1 and cortisol, made up less than 4%.
Ethical approval and considerations

Both trials were performed according to the guidelines of the International Conference on Harmonisation - Good Clinical practice (ICH GCP) and following the ethical principles for medical research of the declaration of Helsinki, October 2000, involving human subjects. The trials were monitored by an independent monitor.

Overall, the randomisation process between different treatment arms raises ethical questions. The probability exists that some of the study participants will have a greater benefit than others depending on the treatment group they are allocated to. There is also a risk that they will have no benefit at all or as a worst case scenario, experience worse outcomes in comparison with the participants in the other treatment arm. The voluntariness of taking part in the trial and the freedom to withdraw at any time was therefore always emphasised and guaranteed. The woman’s integrity and anonymity were respected when reporting data by using a coding system (the randomisation number) for the statistical processing and presentation of the data. Adverse and serious adverse events were registered continuously and resources for dealing with complications were accessible in order to ensure the safety of the participants. Thorough written and oral information was given about the trials and the patient was allowed time for consideration before giving informed consent.

Treatment with tranexamic acid implies no ethical problems since the drug is well established with few risks for complications. It was expected that half of the participants in the trial would probably have an advantage of less bleeding and a lower blood transfusion rate during the operation.

The general and spinal anaesthesia and surgical treatment methods with robotic and abdominal hysterectomy were already implemented in clinical praxis and considered safe, and should therefore not imply an ethical dilemma. Blood samples were collected on seven occasions and could cause discomfort to the women. However, this distress was temporary and of short duration, giving only occasionally a small bruise or a low degree of local inflammation. The amount of blood collected with each sample was 40 ml and most samples were taken during the hospital stay.

The Cyklokapron study was approved by the Regional Ethical Review Board in Linköping, Sweden (Dnr M207-06; approval date: January 23, 2008), and by the Swedish Medical Product Agency (EudraCT 2006-006714-14). The study was registered in ClinicalTrial.gov Protocol Registration System (NCT 00740116) with initial release of August 28, 2008 (http://clinicaltrials.gov).

The Robothyst study was approved by the Regional Ethical Review Board in Linköping, Sweden (Dnr 2011/108-31; approval date: May 19, 2011). The study was registered in ClinicalTrial.gov Protocol Registration System (NCT 01526655) with an initial release of February 6, 2012 (http://clinicaltrials.gov).
Results and Comments

The Cyklokapron study

Blood loss and blood transfusion rate

The baseline demographic and clinical data of the study population are presented in Table 5.

Table 5. Demographic and clinical baseline data according to group of allocation in the Cyklokapron study.

| Characteristic                                      | Tranexamic group (n = 50) | Placebo group (n = 50) | p-value § |
|----------------------------------------------------|---------------------------|------------------------|-----------|
| Age (years)                                        | 63.0 (33-82)              | 64.5 (46-90)           | 0.35      |
| < 60 years of age (no.)                            | 15 (30%)                  | 15 (30%)               |           |
| 60 – 69 years of age (no.)                         | 24 (48%)                  | 17 (34%)               | 0.24      |
| ≥ 70 years of age (no.)                            | 11 (22%)                  | 18 (36%)               |           |
| Height (m)                                         | 1.67 (1.54-1.78)          | 1.63 (1.45-1.74)       | 0.009     |
| Weight (kg)                                        | 71.0 (45.9-106.3)         | 64.3 (46.0-117.0)      | 0.003     |
| Body mass index (kg/m²)                            | 25.9 (17.9-35.2)          | 24.0 (16.7-43.5)       | 0.03      |
| Normal weight (BMI < 25 ) (no.)                    | 19 (38%)                  | 31 (62%)               |           |
| Overweight (BMI 25 - <30) (no.)                    | 25 (50%)                  | 14 (28%)               | 0.05      |
| Obese (BMI ≥ 30) (no.)                             | 6 (12%)                   | 5 (10%)                |           |
| Parity                                             | 2.0 (0-4)                 | 2.0 (0-5)              | 0.85      |
| Smokers (no.)                                      | 8 (16%)                   | 5 (10%)                | 0.55      |
| Low-dose aspirin medication (no.)                   | 7 (14%)                   | 5 (10%)                | 0.76      |
| Cardiac disease (no.)                              | 5 (10%)                   | 1 (2%)                 | 0.20      |
| Arterial hypertension/vascular disease              | 22 (44%)                  | 13 (26%)               | 0.06      |
| Diabetes mellitus (no.)                            | 3 (6%)                    | 7 (14%)                | 0.32      |
| Previous hysterectomy (no.)                        | 6 (12%)                   | 3 (6%)                 | 0.49      |
| Previous laparotomy (no.)                          | 25 (50%)                  | 21 (42%)               | 0.42      |
| PBV †                                              | 4.16 (3.16-5.71)          | 3.87 (2.90-5.71)       | 0.002     |
| RBC transfusion preoperatively (no.)               | 3 (6%)                    | 3 (6%)                 | 1.00      |

Figures denote median (and range), or number (and per cent).
† PBV=0.3561xH³+0.03308xW+0.1833. § Two-sided tests. Mann-Whitney U-test used for continuous data and Pearson Chi²-test and Fisher’s exact test as appropriate used for categorical data. PBV=Predicted Blood Volume.

In spite of the random allocation the tranexamic acid and placebo groups were imbalanced in two of the biometric measures, height and weight, with taller and heavier participants in the tranexamic acid group and consequently also in the predicted blood volume. However, in
randomised trials, imbalance in baseline clinical characteristics arises by chance and thus occurs in 5% (Altman and Dore 1990).

As shown in Table 6 the clinical perioperative data were comparable, revealing no statistically significant differences between the two groups.

Table 6. Perioperative clinical characteristics in the Cyklokapron study.

| Characteristic                                      | Tranexamic group (n = 50) | Placebo group (n = 50) | p-value |
|-----------------------------------------------------|---------------------------|------------------------|---------|
| Haemoglobin, preoperatively (g/L)                   | 123.0 (83-152)            | 118.5 (89-152)         | 0.27    |
| Haemoglobin, day 5 postoperatively (g/L)            | 114.0 (84-151)            | 112.0 (66-136)         | 0.16    |
| Received supplemental tranexamic intraoperatively  | 10 (20%)                  | 10 (20%)               | 1.00    |
| Received desmopressin intraoperatively              | 10 (20%)                  | 13 (26%)               | 0.48    |
| Operation time (minutes)                            | 131 (39-319)              | 123.5 (45-294)         | 0.48    |
| Categorisation of surgery:                          |                           |                        |         |
| “Extensive”                                         | 41 (82%)                  | 35 (70%)               | 0.16    |
| “Diagnostic”                                        | 9 (18.7)                  | 12 (26.7%)             |         |
| Bowel resection                                     | 4 (8%)                    | 5 (10%)                | 1.00    |
| Lymphadenectomy in pelvis and/or para-aortic        | 11 (22%)                  | 6 (12%)                | 0.18    |
| Intra-abdominal drain (no of women)                 | 3 (6%)                    | 2 (4%)                 | 1.00    |
| Final diagnosis:                                    |                           |                        |         |
| Ovarian cancer                                      | 39 (78%)                  | 40 (80%)               | 0.76    |
| FIGO stage I                                        | 3 (7.9%)                  | 2 (5.0%)               |         |
| FIGO stage II                                       | 5 (13.2%)                 | 2 (5.0%)               |         |
| FIGO stage III                                      | 23 (57.9%)                | 33 (82.5%)             |         |
| FIGO stage IV                                       | 8 (21.1%)                 | 3 (7.5%)               |         |
| Borderline ovarian cancer                            |                           |                        |         |
| FIGO stage II/III                                   | 2 (4%)                    | 1 (2%)                 | 1.00    |
| Fallopian tube cancer                               |                           |                        |         |
| FIGO stage III/IV                                   | 4 (8%)                    | 2 (4%)                 | 0.68    |
| Uterus cancer                                       |                           |                        |         |
| FIGO stage IV                                       | 0 (0%)                    | 1 (2%)                 | 1.00    |
| Abdominal cancer                                    |                           |                        |         |
| Urachus cancer                                      |                           |                        |         |
| Retropertitoneal sarcoma                            |                           |                        |         |
| Appendix vermiformis cancer                         |                           |                        |         |
| Benign ovarian neoplasia (cystoma/teratoma)         | 2 (4%)                    | 1 (2%)                 | 1.00    |

Figures denote median (and range), or number (and per cent). FIGO = International Federation of Gynaecology and Obstetrics.

The blood loss outcome variables and transfusions in relation to treatment are presented in Table 7. The total blood loss was statistically significantly lower in the tranexamic acid group compared with the placebo group with a median difference of 210 ml. A 30% reduction in volume of intraoperative bleeding was also reported in a Turkish retrospective study in
surgery for cervical cancer (Celebi, et al. 2006). In prostate cancer surgery with a total blood loss of more than 1,000 ml, the reduction in intraoperative blood loss was similar to our results (Crescenti, et al. 2011).

**Table 7. Outcome of various blood loss measures and transfusion in the Cyklokapron study.**

| Characteristic                              | Tranexamic group (n = 50) | Placebo group (n = 50) | p-value* |
|--------------------------------------------|---------------------------|------------------------|----------|
| Estimated intraoperative blood loss (ml)   | 300 (10-4000)            | 300 (0-2100)           | 0.27     |
| Blood loss in drain (g Hb)                 | 0.0 (0-2.0)               | 0.0 (0-4.9)            | 0.37     |
| External blood loss (g Hb)                 | 34.1 (1.2-456.0)         | 40.0 (0-281.4)         | 0.20     |
| External blood loss (ml)                   | 300 (10-4000)            | 350 (0-2100)           | 0.17     |
| Total blood loss (g Hb)                    | 65.1 (-64.1-392.0)       | 896 (2.0-497.3)        | 0.04     |
| Total blood loss (ml)                      | 520 (-772-3351)          | 730 (23-3855)          | 0.03     |
| Occult blood loss (ml)                     | 230 (-1332-2546)         | 279 (-1435-3609)       | 0.09     |
| Total number of RBC-transfused women       | 15 (30%)                 | 22 (44%)               | 0.07     |
| intra- and postoperatively                 |                           |                        |          |
| Transfused intraoperatively (no.)§         | 11 (22%)                 | 10 (20%)               | 0.04     |
| Transfused postoperatively (no.)§          | 6 (12%)                  | 14 (28%)               | 0.03     |
| Plasma transfusion (no. of women)          | 4 (8%)                   | 9 (18%)                | 0.12     |

Figures denote median (and range), or number (and per cent).

* Mann-Whitney U-test used for continuous data and Pearson χ²-test and Fisher’s exact test as appropriate used for categorical data.

§ Two women in each group received blood transfusions intraoperatively as well as postoperatively.

All p-values are based on one-sided tests.

The reduction in bleeding volume in cancer surgery seems to be much lower than those in orthopaedic surgery (Alshryda, et al. 2011). Estimation of blood loss in ovarian cancer patients can be misleading because of the possibility of postoperative effusion of ascites caused by peritoneal resections or residual disease at the end of the operation, with substantial haemodynamic changes resulting in a state of haemoconcentration and underestimation of the total blood loss (Eisner, et al. 1990, Chi, et al. 2010). Another explanation for the low reduction could be the pathological angiogenesis and neovascularisation in ovarian cancer with bulky and widespread dissemination of the tumour, increased bleeding intraoperatively, and a lower efficacy of tranexamic acid. Also, the possible altered state of coagulation and fibrinolysis in cancer patients could interfere with the efficacy of tranexamic acid. The dosage and timing of tranexamic acid administration could have an impact on blood loss. We used a single dose treatment of 15 mg/kg body weight intravenously based on the experience from a previous study conducted in Linköping in orthopaedic surgery (Johansson, et al. 2005) and also because it was similar to the dosage used in the study of Crescenti et al. in prostate cancer. Recently, a small study has been published in abdominal tumour surgery investigating tranexamic acid given as a single dose intravenously with a postoperative infusion for four hours compared with placebo. It seemed that a single dose of tranexamic acid before surgery...
with continuous infusion for four hours postoperatively significantly reduced the postoperative bleeding within 24 hours (Prasad, et al. 2018).

In our study, all other outcome measures of blood loss were, numerically, but not statistically significantly, lower in the tranexamic acid group than in the placebo. The use of RBC transfusions was more frequent in the placebo group, with only the postoperative RBC transfusion as an exception with a significantly lower rate in favour of tranexamic acid in the univariate analyses.

Because a clear transfusion protocol in the study was lacking, we considered it necessary in the multivariate analysis to adjust the primary outcome of blood transfusion rate for the confounding factors in the decision-making about giving a transfusion. We adjusted the blood transfusion rate for age, cardiac disease and the extent of the surgery. In the multivariate logistic regression the differences in RBC transfusion rate between the study groups reached statistical significance with a significantly lower rate in the tranexamic acid group. For the total number of women receiving RBC transfusion intra- and postoperatively the adjusted OR was 0.44 (upper 95% CI=0.97), \( p=0.02 \) and for the number of women transfused postoperatively the equivalent figures were OR=0.27 (upper 95% CI=0.75), \( p=0.02 \). The median estimated blood loss perioperatively was 600 ml (range 200-4000 ml) for those who had RBC transfusions and 200 ml (range 0-1000 ml) for those who did not have transfusions (Mann Whitney U-test, \( p<0.001 \)). Similar results were shown in the systematic review article and meta-analysis by Montroy et al. about tranexamic acid in cancer patients showing a reduced pooled relative risk of blood transfusion of 48 % compared to placebo (Montroy, et al. 2017).

In the per protocol analysis, in the comparison of the women that de facto received the study medication, the results were similar concerning the blood loss outcomes, but in transfusion rates the difference in the total number of women receiving transfusions intra- and postoperatively did not reach statistical significance. The trial protocol allowed the use of supplemental tranexamic acid if the bleeding during surgery was clinically considered unacceptable. This could bias the results although for the participants who had supplemental tranexamic acid the estimated blood loss perioperatively was median 500 ml (range 200-4000 ml) compared with 250 ml (range 0-1500 ml) for those who did not receive supplemental tranexamic acid (Mann-Whitney U-test, \( p = 0.02 \)). This might indicate that those patients were “easy-bleeders” and received the supplemental dose according to the trial protocol and clinical praxis.

In total 38 units and 53 units of RBC, respectively, were given to 15 women in the tranexamic acid group and to 22 women in the placebo group. The median number of transfused units among those who received RBC transfusions was two in both groups (range 1-6 and range 1-7, respectively) and did not differ significantly between the groups (Mann-Whitney U-test, \( p = 0.46 \)). The absolute risk reduction in RBC transfusions was 14% (95% CI: -4.7% to 32.7%) thus the number of women necessary to treat with tranexamic acid in order to avoid RBC transfusion in one woman, was seven. The distribution of the number of units RBC given is shown in Figure 10.
Figure 10. Distribution of the number of units of RBC transfused in 50 women receiving tranexamic acid and 50 women receiving placebo in the Cyklokapron study.

Overall postoperative complications are depicted in Table 8. Re-admission, re-operation and infection rates were evenly distributed between the groups. However, when adjusted for confounding factors, re-admission was significantly more frequent in the tranexamic acid group than in the placebo group. We find no reasonable clinical explanation for this result. Re-admission for the women with infectious complications occurred more frequently in the tranexamic acid group compared with placebo. Statistically, no significant difference could be observed between the groups concerning postoperative infections. This is in contrast to studies supporting tranexamic acid as immuno-modulatory with the ability to reduce postsurgical infection rates (Draxler, et al. 2019). However, our study was not powered for postoperative complications in general.

Thromboembolic events occurred in seven women (7%), two in the tranexamic acid group and five in the placebo group; an incidence that could be expected in ovarian cancer patients postoperatively (Tateo, et al. 2005). Two of the events were symptomatic and diagnosed prior to the five-week follow-up visit. The other five thromboembolic events were asymptomatic and were detected at the follow-up ultrasound assessment. Fifty-six women (56%) participated in the duplex ultrasound assessment of the legs, which was an optional investigation according to the trial protocol. Unfortunately, this indicates a high risk of bias for the outcome of thromboembolic complications (Kietpeerakool, et al. 2016). With the knowledge that some women can have a thrombosis without symptoms it is strongly recommended that the next tranexamic acid study include all participants in a Doppler ultrasound investigation, regardless of symptoms.
Table 8. Complications within five weeks after surgery in the Cyklokapron study.

| Characteristic                                | Tranexamic group (n = 50) | Placebo group (n = 50) | Univariate analysis* | Multiple logistic regression analysis* |
|-----------------------------------------------|---------------------------|------------------------|----------------------|----------------------------------------|
| Thromboembolic events (no. of women)         |                           |                        |                      |                                        |
| Arterial thrombosis a. poplitea              | 0                         | 1                      |                      |                                        |
| Deep venous thrombosis in leg                | 1                         | 1                      |                      |                                        |
| Superficial venous thrombosis in leg         | 1                         | 0                      |                      |                                        |
| Muscle vein thrombosis in leg                | 0                         | 3                      |                      |                                        |
| Re-admission (no of women)                   | 11                        | 4                      | 0.22                 | 0.36 (0.05–2.72)                       | 0.32 |
| Re-operations (no. of women)                 | 5                         | 6                      | 1.00                 | 0.66 (0.17–2.59)                       | 0.55 |
| Wound rupture                                | 4                         | 1                      |                      |                                        |
| Intra-abdominal bleeding                      | 0                         | 2                      |                      |                                        |
| Peritonitis (bile leakage)                   | 1                         | 0                      |                      |                                        |
| Bowel perforation                            | 0                         | 1                      |                      |                                        |
| Pelvic abscess                               | 1                         | 0                      |                      |                                        |
| Arterial thrombosis a. poplitea              | 0                         | 1                      |                      |                                        |
| Infections (no. of women)                    | 10                        | 16                     | 0.17                 | 0.41 (0.14–1.26)                       | 0.12 |
| Sepsis                                       | 1                         | 2                      |                      |                                        |
| Pneumonia                                    | 1                         | 2                      |                      |                                        |
| Wound infection                              | 4                         | 5                      |                      |                                        |
| Urinary tract infection                      | 1                         | 1                      |                      |                                        |
| Gastroenteritis                              | 1                         | 1                      |                      |                                        |
| Peritonitis                                  | 2                         | 1                      |                      |                                        |
| Fever, unknown focus                         | 0                         | 2                      |                      |                                        |
| Pelvic infection                              | 0                         | 2                      |                      |                                        |

* Univariate analysis; Pearson Chi2-test or Fisher’s exact test, as appropriate. Two-sided test.

* Multiple logistic regression analysis: adjusted for BMI, cardiovascular disease, intraoperative supplement of tranexamic acid, and re-operations. Thromboembolic events and re-admission also adjusted for intra- and postoperative transfusions, and postoperative infections. Infections also adjusted for intra- and postoperative transfusions. Re-operation also adjusted for estimated bleeding volume intraoperatively, and intraoperative complications.
The Robothyst study

HRQoL and postoperative symptoms

The randomisation process worked well since there were no significant differences in the demographic and descriptive data demonstrated in Table 9. The intra- and postoperative data including complications as shown in Table 10 reveal a balanced distribution between the groups, except for a significantly shorter operation and anaesthesia time for the abdominal group.

Table 9. Demographic and descriptive data in the Robothyst study.

|                      | Robotic hysterectomy (n=25) | Abdominal hysterectomy (n=25) |
|----------------------|-----------------------------|-------------------------------|
| Age (years)          | 68 (38-83)                  | 67 (45-85)                   |
| Body mass index (kg/m²) | 28.2 (21.5-54.1)          | 28.0 (19.4-37.8)              |
| BMI < 25 kg/m²       | 7 (28%)                    | 8 (32%)                      |
| BMI 25-29.9 kg/m²    | 8 (32%)                    | 10 (40%)                     |
| BMI 30-35 kg/m²      | 6 (24%)                    | 5 (20%)                      |
| BMI > 35 kg/m²       | 4 (16%)                    | 2 (8%)                       |
| Parity               | 2 (0-5)                    | 2 (0-5)                      |
| Smokers              | 4 (16%)                    | 0 (0%)                       |
| Previous laparotomy  | 13 (52%)                   | 8 (32%)                      |
| Comorbidity:         |                            |                              |
| Cardiovascular disease | 10 (40.0%)                | 11 (44%)                     |
| Pulmonary disease    | 3 (12%)                    | 3 (12%)                      |
| Diabetes mellitus    | 0 (0%)                     | 4 (16%)                      |
| Previous breast cancer | 3 (12%)                | 3 (12%)                      |
| Current medication:  |                            |                              |
| Antidepressant/sedative | 2 (8%)                   | 3 (12%)                      |
| Analgesics           | 5 (20%)                    | 2 (8%)                       |
| ASA classification:  |                            |                              |
| Class I              | 9 (36%)                    | 11 (44%)                     |
| Class II             | 15 (60%)                   | 13 (52%)                     |
| Class III            | 1 (4%)                     | 1 (4%)                       |
| EQ-5D health index preoperatively | 0.81 (0.12-1.00) | 0.82 (0.12-1.00) |
| HADS Anxiety         |                            |                              |
| No anxiety           | 13 (52%)                   | 15 (60%)                     |
| Mild-moderate anxiety | 9 (36%)                 | 6 (24%)                      |
| Severe anxiety       | 3 (12%)                    | 4 (16%)                      |
| Depression           |                            |                              |
| No depression        | 21 (84%)                   | 21 (84%)                     |
| Mild-moderate depression | 4 (16%)               | 4 (16%)                      |
| PSQ total score      | 2.9 (1.6-6.6)              | 3.3 (0.4-6.6)                |
| PSQ minor score      | 2.1 (0.6-5.0)              | 2.3 (0.3-7.3)                |
| PSQ moderate score   | 4.4 (1.0-9.7)              | 4.4 (0.6-7.3)                |

Figures denote median (and range), or number (and per cent).
ASA, American Society of Anesthesiologists physical status classification system; BMI, body mass index;
EQ-5D, EuroQol Group form; HADS, Hospital Anxiety and Depression Scale; PSQ, Pain Sensitivity Questionnaire.
Table 10. Peri- and postoperative data in the Robothyst study.

| Operation time\(^a\) (minutes) | 70 (48-125) | 56 (41-104) | 0.048 |
|---------------------------------|-------------|-------------|-------|
| Estimated intraoperative blood loss (ml) | 50 (20-150) | 50 (10-250) | 0.68 |
| Anaesthesia times (minutes) | 147 (112-239) | 115 (70-177) | <0.0001 |
| Time in post anaesthesia care unit (hours) | 4.4 (2.7-13.3) | 5.2 (2.3-11.5) | 0.34 |
| Length of hospital stay (de facto) (hours) | 53 (30-60) | 51 (32-98) | 0.16 |
| Length of hospital stay (when discharge criteria met) (hours) | 36 (30-60) | 36 (30-60) | 0.27 |
| Final histopathological diagnosis | FIGO grade 1 EC: 15 (60%) | 11 (46%) | 0.44\(^a\) |
| | FIGO grade 2 EC: 9 (36%) | 10 (42%) | 0.25 |
| | FIGO grade 3 EC: 1 (4%) | 3 (12%) | |
| Surgical FIGO stage | IA: 18 (72%) | 15 (63%) | |
| | IB: 4 (16%) | 7 (29%) | 0.70\(^a\) |
| | II: 1 (4%) | 1 (4%) | |
| | IIIA: 2 (8%) | 1 (4%) | |
| Adverse events during hospital stay (no. of women) | 2 (8%) | 5 (21%) | 0.25\(^b\) |
| Bladder injury | 1 | | |
| Spinal puncture not possible | 1 | 2 | |
| Intubation difficulties | | 1 | |
| Vaginal vault haematoma | | 1 | |
| Red blood cell transfusion | | 1 | |
| Urinary catheter not settled at discharge | | 1 | |
| Neuralgia | | 1 | |
| Adverse events after discharge until follow-up (no. of women) | 6 (24%) | 10 (42%) | 0.19\(^a\) |
| Re-operation due to vaginal vault bleeding | | 1 | |
| Minor wound complications\(^§\) (wound infections) | | 6 (2) | |
| Lower urinary tract infection | 2 | 3 | |
| Constipation, ileus suspicion | 2 | | |
| Pain/neuralgia | 4 | 1 | |

Figures denote median (and range), or number (and per cent). EC=endometrioid adenocarcinoma. FIGO=International Federation of Gynaecology and Obstetrics. \(^#\) Time from skin open to skin closure; \(^*\)Mann-Whitney U-test applied for continuous data and a Pearson Chi\(^2\)-test or \(^b\) Fisher’s exact test for categorical data. \(^\$\) Superficial infection, seroma and superficial wound rupture.

Overall, the EQ-5D showed a significantly faster recovery of the HRQoL in the robotic hysterectomy compared with abdominal (Figure 11). The women recovered to their preoperative level on the fifth postoperative day whereas the women in the abdominal group had recovered to their preoperative state after 28 days. The difference in daily measurements of EQ-5D index was significant on almost all occasions until postoperative day 28 as shown in the Fisher’s PLSD post hoc test.
Figure 11. The EQ-5D weighted health state index in relation to occasion of measurement in the Robothyst study. Plots represent means and bars represent 95% confidence intervals. Repeated measures ANOVA from day 0 after surgery to the six-week assessment. No significant difference was observed between the two groups at baseline preoperatively (Mann-Whitney U-test). AH=abdominal hysterectomy; RH=robotic hysterectomy.
Because we assumed that perioperative complications could influence the patients’ well-being and health state, and more complications numerically were present in the abdominal group, we adjusted the EQ-5D index for this confounding factor. The EQ-5D index between the women in the robotic and abdominal hysterectomy groups did not differ significantly in the period from day 0 to day 4 during hospitalisation with and without adjustment for perioperative complications (Figure 12). But in the period from day 5 to day 42 after discharge from the ward the women in the robotic hysterectomy group had a significantly faster recovery measured by the EQ-5D index than the abdominal group. When adjusted for postoperative complications, the women recovered to their preoperative EQ-5D level nearly two weeks earlier than the abdominal hysterectomy group, at three and five weeks respectively.

The HRQoL as assessed by the SF-36 preoperatively and at the six-week postoperative visit showed that the groups had recovered evenly after six weeks (Table 11) except for the subscales of general health and social functioning. The women in the robotic hysterectomy group showed a greater improvement than the women in the abdominal hysterectomy group in these subscales. When adjusted for complications on any occasion, only general health remained statistically significant (Mann-Whitney U-test, \( p=0.04 \)) in the group without complications (RH, \( n=17 \) and AH, \( n=12 \)).

Limited data are available on HRQoL. Most of the focus in articles about robotic surgery has been on surgical aspects and complications (Park, et al. 2016). Other trials conducted as single arm studies on HRQoL in robotic surgery for endometrial cancer showed similar outcomes as our trial, with decreased quality of life and negatively affected postoperative symptoms one week after robotic surgery compared to baseline and a return to the preoperative level within five or six weeks after surgery (Arms, et al. 2015, Herling, et al. 2016a). Ferguson et al. investigated prospectively HRQoL between laparoscopic, robotic and open surgery for endometrial cancer and showed similar results as those presented in our study, with improved HRQoL three weeks postoperatively for minimally invasive surgery compared to open surgery (Ferguson, et al. 2018). In contrary to our trial, that study was not performed in an ERAS programme and the mean EQ-5D index was not adjusted for postoperative complications, which seem to have a substantial impact on the outcomes.
Figure 12. EQ-5D health index from Day 0 to Day 42 in the Robothyst study. Plots represent means and bars represent 95% confidence intervals. Repeated measures ANOVA. Crude and adjusted p-values. The EQ-5D health index on Day 0 - 4 was adjusted for complications during hospital stay and on Day 5 - 42 was adjusted for complications during hospital stay and complications after discharge. AH = abdominal hysterectomy; RH = robotic hysterectomy.
Table 11. SF-36 subscales and summary scores in the Robothyst study.

| SF-36 subscales | Time lapse | Baseline | Day 42 postoperatively | Difference between the postoperative and baseline assessments | p-value* |
|-----------------|------------|----------|------------------------|--------------------------------------------------------------|----------|
|                 | Robotic hysterectomy | Abdominal hysterectomy | Robotic hysterectomy | Abdominal hysterectomy | Robotic hysterectomy | Abdominal hysterectomy |               |
| Physical functioning | 82.8 (20.9) | 81.3 (18.7) | 80.6 (23.0) | 75.6 (20.2) | -2.2 (16.0) | -5.6 (10.5) | 0.25 |
| Role physical | 74.0 (37.8) | 79.2 (36.6) | 54.0 (44.3) | 41.7 (42.1) | -20.0 (44.5) | -37.5 (41.7) | 0.17 |
| Bodily pain | 81.0 (21.6) | 70.4 (27.8) | 75.9 (18.2) | 65.4 (27.2) | -5.1 (15.5) | -5.0 (31.5) | 0.94 |
| General health | 71.1 (18.4) | 77.8 (21.3) | 76.0 (17.0) | 75.4 (20.5) | 4.9 (14.9) | -2.5 (11.2) | 0.02 |
| Vitality | 73.8 (19.0) | 66.5 (27.2) | 70.6 (19.2) | 61.5 (19.5) | -3.2 (18.5) | -5.0 (24.8) | 0.61 |
| Social functioning | 90.0 (15.7) | 82.8 (20.8) | 94.0 (11.5) | 78.1 (19.9) | 4.0 (13.8) | -4.7 (16.4) | 0.03 |
| Role emotional | 80.0 (33.3) | 88.9 (25.4) | 77.3 (41.6) | 86.1 (27.7) | -2.7 (27.1) | -2.8 (32.5) | 0.52 |
| Mental health | 76.6 (18.8) | 72.2 (19.0) | 87.4 (11.3) | 79.3 (17.3) | 10.7 (13.3) | 7.2 (19.6) | 0.24 |
| Physical component summary score | 48.6 (9.8) | 48.2 (11.9) | 44.7 (9.9) | 41.1 (11.3) | -4.0 (7.3) | -7.1 (8.7) | 0.30 |
| Mental component summary score | 49.4 (9.1) | 48.2 (11.1) | 53.2 (7.6) | 50.8 (8.4) | 3.8 (7.1) | 2.7 (10.8) | 0.44 |

Figures indicate mean (1 SD). Scoring scale between 0-100. A high score represents a better HRQoL.
No significant differences were observed in subscales between the two groups at baseline preoperatively (Mann-Whitney U-test).
* Mann-Whitney U-test, p-values adjusted for ties.
After discharge from the ward the women in the robotic group presented significantly fewer postoperative symptoms according to the SPSQ symptom sum score than the women in the abdominal group when adjusted for complications (Figure 13). It seemed reasonable to adjust postoperative symptoms for the confounder of postoperative complications as this factor could influence the results. Generally, based on clinical experience it seemed obvious that women with postoperative complications experience more postoperative symptoms after surgery than women without complications.

The reported postoperative pain intensity at peak did not differ significantly between the groups during the hospitalisation from day 0 to day 4, but was significantly lower in the robotic group after discharge from the ward in the period from day 5 to day 42. After adjustment for complications the significance vanished. In these periods no significant differences between the groups were seen for the reported average pain intensity.

The consumption of opioids after the operation was equally low in both groups and remained very low from day 1 and onwards. The consumption of non-opioid analgesics revealed no significant differences between the groups.

The absence of statistically significant differences between the groups during hospitalisation in the SPSQ symptom sum score, postoperative pain and the consumption of analgesics could indicate a positive effect of using an ERAS protocol with an intrathecal spinal analgesia before induction of the general anaesthesia, giving both groups an equal and optimal treatment of perioperative symptoms (Lavand'homme and De Kock 2006).

The equality of these outcomes might also indicate the possibility of an awareness bias in the robotic hysterectomy group regarding the potential benefits of robotic surgery, as after discharge from the ward the women in the robotic group rated the SPSQ symptom sum score lower and the EQ-5D health index higher, indicating a faster recovery despite the same symptoms initially being present in both groups.

Length of hospital stay, defined from the time of arrival in the operating theatre to the discharge from the ward or to when the discharge criteria were met was similar between the two groups (as shown previously in Table 10). For the women who had no perioperative complications during the hospital stay (RH, n=23 and AH, n=19) the time to meet the discharge criteria was significantly lower in the robotic group (median (range) 36 hours (30-60) vs 36 hours (36-60), Mann-Whitney U-test adjusted for ties, p=0.03).

This result is in contrast with most other robotic trials in gynaecological cancer (Park, et al. 2016, Kristensen, et al. 2017), most of which have not been performed in an ERAS setting. It is difficult to compare hospital stay because of uneven definitions of hospital stay and differences in how the results are expressed, often in days and not in hours. With a short duration of hospital stay, it seems better to use hospital stay in hours than in days. Both the occurrence of complications and the ERAS programme play a role in the length of hospitalisation. Perioperative complications had a negative effect on hospital stay and HRQoL as shown by our trial data. The ERAS programme has been shown to influence not only hospital stay but also the occurrence of perioperative complications, both in a positive manner (Gustafsson, et al. 2016).
Repeated measures ANOVA
Timing  Main effect between hysterectomy groups Main effect over time Interaction effect
Day 0 to Day 4  
Crude  p=0.02  p<0.0001  p=0.91
Adjusted  p=0.06  p<0.0001  p=0.97
Day 5 to Day 42  
Crude  p<0.01  p<0.0001  p=0.16
Adjusted  p=0.02  p=0.04  p=0.36

Figure 13. SPSQ postoperative symptom sum score from day 0 to day 42. Plots represent mean sum score and bars represent 95% confidence interval. Repeated measures ANOVA. Crude and adjusted p-values. The SPSQ sum scores on Day 0-4 were adjusted for complications during hospital stay and on Day 5-42 were adjusted for complications during hospital stay and complications after discharge.
AH = abdominal hysterectomy; RH = robotic hysterectomy. SPSQ = Swedish Postoperative Symptom Questionnaire.
Recently, Wijk et al. published data from an international observational multicentre study of more than 2000 patients undergoing elective gynaecological surgery and found a positive association between increased compliance with the ERAS guidelines and a shorter length of hospital stay, regardless of the magnitude of the operation. They also observed that the risk of having a complication was lower when the compliance with the ERAS guidelines was high (Wijk, et al. 2019).

When using standardised discharge criteria checked twice daily, we found that the average length of hospital stay, from hour of arrival in the operating theatre to the time the discharge criteria were fulfilled, could be minimised to 36 hours in both groups compared with the de facto hospital stay of 53 hours in the robotic group and 51 hours in the abdominal group. Theoretically most of the women could have been discharged the next evening after surgery but “chose” not to return home for other reasons. This could have been caused by the blood sample collection on day 2 in accordance with the study protocol, which may have influenced participants to stay until then and thus might have led to an unnecessary longer stay in the ward for these participants.

None of the women in the Robothyst study needed conversion of the robotic operation to an open surgery. No major complications were observed in the robotic group, whereas in the abdominal hysterectomy group, one woman needed a re-operation due to vaginal vault bleeding and two readmissions occurred because of symptoms of bowel obstruction. No statistically significant difference was seen in occurrence of minor complications, although they were numerically more prevalent in the abdominal hysterectomy group, as shown in Table 10. The Kaplan-Meier curve over time from discharge from the ward to the occurrence of a postoperative complication revealed no significant difference between the groups (Figure 14).

Figure 14. The Kaplan-Meier curve of the cumulative proportion of women without complications in the Robothyst study in relation to time after discharge to the occurrence of the adverse event in the two groups. Comparison was performed by means of the Cox Proportional Hazard Model. Results presented as hazard ratio (HR) and 95% confidence interval (CI).
The longer operation times for the robotic hysterectomy compared with the abdominal operation found in our study were also reported in previously published studies and are comparable to the times in our trial (Mok, et al. 2012, O'Malley, et al. 2015). The learning curve effect is important when incorporating a new technique. Learning curves for the robotic procedure have been discussed. It is not only the role for the robotic surgeon to optimise the surgical resource; the whole operating team has an impact. Learning curves for the entire surgical team have been presented with a wide variety of numbers of operations which can vary from about ten to a larger number of procedures (Sandadi, et al. 2014, Maenpaa, et al. 2015).

Robotic surgery was introduced in gynaecological surgery in our department in 2010 with access to the robotic system one day weekly. Although the single robotic surgeon in the study had performed more than 50 robotic hysterectomies prior to the start of the trial, still a potential surgical improvement could be seen in surgery time during the study period 2012-2016 with a significant difference in the robotic group (Figure 15).

![Figure 15](image.png)

**Figure 15.** Surgery time (in minutes) in robotic (RH) and abdominal hysterectomy (AH) during the course of the Robothyst study 2012-2016.

Abdominal hysterectomy with bilateral salpingo-oophorectomy is a routine procedure and six accredited gynaecological oncology surgeons performed the operations. The mean surgery time for the abdominal operation did not change during the course of the study. On the contrary, the time for preparation and closing the operating theatre increased over time in the robotic group, although not significantly, whereas the corresponding time decreased significantly over time in the abdominal group (Figure 16). A possible explanation could be the routines of two teams working with different areas of responsibility and previous experience. Our results confirm that learning curves are present for both surgeons and the staff in the operating theatre. Thus, it is important to optimise the entire process in the operating theatre for all staff members of the surgical team. In the present study, our
findings may indicate a possible bias in the health economic analysis, as the time in the operating theatre for preparation and closing the operating theatre did not seem to be optimised in the robotic group. The reasons for these deviations need further analysis and are important for optimising the robotic hysterectomy, not least from the health care and societal perspectives.

![Figure 16](image)

**Figure 16.** Time in the operating theatre (in minutes) for preparation and closing only, for the robotic (RH) and abdominal hysterectomy (AH) during the course of the Robothyst study 2012-2016.

For both the robotic and abdominal hysterectomy group the anaesthesia time and total time in the operating theatre did not change significantly over time during the course of the Robothyst study between 2012 and 2016. However, between the groups there were significant differences concerning anaesthesia time ($p<0.0001$), surgery time ($p=0.048$) and total time in the operating theatre ($p<0.0001$).

**Tissue damage and inflammation**

Blood samples were collected on seven specified occasions in the perioperative period, starting one week preoperatively and ending six weeks postoperatively. The response from each inflammatory and tissue damage marker differs in their specific time course. Our choice of measurement times is a compromise between exploring the full perioperative period and the detection of the individual marker’s peaks in the short and long-term. From our design, we were not able to detect neither nadir or peak levels but we argue that we may have obtained a clinically relevant picture of the course of inflammatory, immunological, hormonal and tissue damage markers.

The levels and changes over time of the seven markers are presented in Figure 17.
T1=1w before op; T2=just before op; T3=2h post-op; T4=24h post-op; T5=48h post-op; T6=1w post-op; T7=6w post-op
Occasion of measurement

**Time 1**: 1 week before surgery  
**Time 2**: On the day of operation, before surgery  
**Time 3**: 2 hours postoperatively  
**Time 4**: 24 hours postoperatively  
**Time 5**: 48 hours postoperatively  
**Time 6**: 1 week postoperatively  
**Time 7**: 6 weeks postoperatively

### Repeated measures analysis of variance (p-values)

| Marker     | Main effect between groups | Effect over time | Interaction effect |
|------------|----------------------------|------------------|--------------------|
| hsCRP      | 0.03                       | <0.0001          | 0.02               |
| WBC        | <0.01                      | <0.0001          | <0.0001            |
| Thrombocytes| 0.83                      | <0.0001          | <0.01              |
| IL-6       | 0.03                       | <0.0001          | <0.001             |
| CK         | 0.03                       | <0.0001          | <0.01              |
| HMGB1      | 0.07                       | <0.0001          | <0.01              |
| Cortisol   | 0.06                       | <0.0001          | <0.01              |

### Tukey HSD post hoc test (p-values)

| Timing          | Time 2 | Time 3 | Time 4 | Time 5 | Time 6 | Time 7 |
|-----------------|--------|--------|--------|--------|--------|--------|
|                 | 1w     | 2h     | 24h    | 48h    | 1w     | 6w     |
| Before op       | Post-op| post-op| post-op| post-op| post-op| post-op|
| hsCRP           |        |        |        |        | 0.02   | <0.001 |
| WBC             |        | <0.0001|        |        |        |        |
| IL-6            |        | <0.01  |        |        |        |        |
| CK              |        |        |        | <0.0001|        |        |
| HMGB1           | 0.05   |        |        |        |        | <0.0001|
| Cortisol        |        |        |        |        | <0.0001|        |

**Figure 17.** Diagrams showing the levels of the markers of inflammation and tissue damage in relation to timing and group in the Robothyst study. Plots represent means and bars represent 95% confidence intervals. The table below presents the results of the repeated measures ANOVA (from Time 2 to Time 7 for all except IL-6, which was from Time 3 to Time 5) and the Tukey honestly significant difference post hoc tests for pairwise comparisons. Only the p-values of significant differences in the post hoc tests are presented.
The results demonstrated a significantly lower response in the inflammatory, immunological, stress and tissue damage markers hsCRP, WBC, IL-6, cortisol and CK after robotic hysterectomy in an ERAS programme treating early endometrial cancer compared with abdominal hysterectomy. The difference between the markers was of short duration and evened between one and two days after the operation. All markers showed significant variation over time and significant interaction effects between groups and measurement times.

Our findings of increased inflammation caused by elevated hsCRP, WBC and IL-6 with a differentiated response depending on mode of surgery are consistent with other trials in endometrial cancer surgery and in colorectal surgery, as is likewise the significant thrombocytosis we found, independent of the mode of surgery (Pilka, et al. 2016, Zawadzki, et al. 2017, Mohamud, et al. 2018).

We did not find any studies about the appearance of CK in the blood as an indirect marker of muscle damage after robotic surgery. Earlier trials investigated CK and the complication of rhabdomyolysis following robotic surgery (Karaoren, et al. 2017). None of the participants in our trial had symptoms of this rare postoperative complication. The significantly elevated level of CK in the abdominal hysterectomy group compared with the robotic hysterectomy group implied that more muscle damage occurred after the abdominal surgery.

The levels of HMGB1 did change significantly over time but did not differ significantly between the two modes of surgery. This finding is in contrast with other trials showing an increased HMGB1 level released from necrotic or injured cells two to six hours after severe injury in trauma patients or after abdominal surgery in correlation with the duration of the operation (Peltz, et al. 2009, Maca, et al. 2017). This could imply that the extent of the overall tissue damage after hysterectomy, independent of the mode of surgery, in our trial was not sufficient to result in an elevated level of the marker. Another explanation could be that the method of analysis was not sufficiently sensitive to detect low levels.

We observed a sustained high level of cortisol two hours after the abdominal surgery but not after robotic hysterectomy comparable to the preoperative high level just before the operation for both groups. This was also reported by Wijk et al. who demonstrated higher cortisol levels three hours after abdominal hysterectomy compared to robotic. However, the levels just before the operation were not analysed in Wijk’s study and it was not clear when the levels evened (Wijk, et al. 2018). The study by Khoo et al. in redefining the stress cortisol response to surgery revealed a positive correlation of surgical severity with the observed peak serum cortisol and that the cortisol levels tended to return to baseline on postoperative day one, even in major surgery (Khoo, et al.). In our trial in spite of the efforts of the ERAS programme in opposing surgical stress through the neuroendocrine pathway resulting in lower cortisol values (Lavand'homme and De Kock 2006, Day, et al. 2015), the surgical trauma itself following abdominal hysterectomy might have caused a persistently high cortisol level two hours after open surgery. This was probably induced by the effect of an increased IL-6 level on the hypothalamic pituitary adrenal pathway. The high cortisol level two hours after the
operation was an independent factor for the elevated levels of WBC (p<0.01) but not for any of the other markers in the repeated measures ANOVA when adjusted for cortisol at time 3.

Cost-effectiveness and QALY

Participant characteristics and resource utilisation are shown in Table 12, and revealed no statistically significant differences between the groups except for a shorter total time in the operating theatre, and also shorter operation and anaesthesia time for the abdominal group.

Table 12. Participant characteristics and resource utilisation in the Robothyst study

|                                | Robotic hysterectomy (n=25) | Abdominal hysterectomy (n=24) |
|--------------------------------|-------------------------------|-----------------------------|
| Age (years)                    | 68 (38-83)                    | 67 (45-85)                  |
| Body mass index (kg/m²)        | 28.2 (21.5-54.1)              | 28.0 (19.4-37.8)            |
| Parity                         | 2 (0-5)                       | 2 (0-5)                     |
| ASA classification             |                               |                             |
| Class I (no. of women)         | 9 (36%)                       | 11 (46%)                    |
| Class II (no. of women)        | 15 (60%)                      | 12 (50%)                    |
| Class III (no. of women)       | 1 (4%)                        | 1 (4%)                      |
| Employed (no. of women)        | 8 (32%)                       | 9 (37%)                     |
| Time of surgery (minutes)#     | 70 (48-125)                   | 56 (41-104)                 |
| Estimated per-operative blood loss (mL) | 50 (20-150)                  | 50 (10-250)                 |
| Time of anaesthesia (minutes)# | 147 (112-239)                 | 115 (70-177)                |
| Time in operating theatre (minutes)# | 176 (140-264)              | 145 (100-215)               |
| Time in PACU (hours)           | 4.4 (2.7-13.3)                | 5.2 (2.0-11.5)              |
| Length of hospital stay, de facto (hours) | 53 (30-60)                  | 51 (32-98)                  |
| Length of hospital stay, discharge criteria were met (hours) | 36 (30-60)                  | 36 (30-60)                  |
| Sick leave (no. of women)      | 8 (32%)                       | 9 (37%)                     |
| Sick leave (days)              | 25 (6-31)                     | 31 (18-47)                  |
| Receiving informal care (no. of women) | 12 (48%)                     | 10 (42%)                    |
| Informal care (hours)          | 5.5 (1-55)                    | 16.8 (1-57)                 |
| Readmissions to hospital (no. of patients) | 0 (0%)                      | 3 (12.5%)                   |
| Unplanned visits to physician (no. of visits/ no. of patients) | 3/1 (4%)                     | 12/7 (29.2%)                |
| Unplanned visits to nurse (no. of visits/ no. of patients) | 3/2 (8%)                     | 14/6 (25%)                  |

Figures denote median (and range) or number (and percent). ASA, American Society of Anesthesiologists physical status classification system; PACU, Post Anaesthesia Care Unit. #Time of surgery (p=0.048), anaesthesia time (p<0.0001) and total time in operating theatre (p<0.0001) differed significantly between the groups in the univariate analysis.
Two thirds of the women were retired. There was no significant difference concerning number of days on sick leave or hours of informal care provided between the study groups. Moreover, the number of re-admissions to the hospital or unplanned visits outside the study protocol did not reach statistical significance. However the number of unplanned visits was numerically higher in the abdominal group.

Table 13 demonstrates the proportional total costs for the robotic and abdominal hysterectomy group respectively, divided into direct (or hospital) and indirect (or societal) costs.

The EQ-5D-3L health state index measured day-by-day the first week and then once weekly until day 42 postoperatively in the robotic and abdominal hysterectomy group is represented in Figure 11 (page 49). Women who had robotic hysterectomy had a significantly faster recovery of the HRQoL than the abdominal hysterectomy group. The robotic hysterectomy women recovered to their preoperative level nearly two weeks earlier than the abdominal group when adjusted for complications. To calculate direct and indirect costs and estimate QALYs, we used the non-adjusted EQ-5D because we wanted to access the *de facto* proportional cost between the two groups during the actual hospitalisation and postoperative period.

The gain in QALY weight for the robotic group was 0.87, and 0.72 for the abdominal group. Each woman in the robotic group gained 0.018 QALYs compared with the abdominal group for a time period of six weeks. The ICER was calculated by dividing the cost differences per treatment method by the difference in QALY for each group, showing a cost for one QALY gained in the robotic group of $13,085/0.018 = \text{SEK 726,944}$ for 300 robotic operations, and \text{SEK 512,556} for 500 robotic operations a year.

Our trial is the first in gynaecological cancer surgery with a cost-utility analysis, usually called a cost-benefit analysis with QALY as an outcome measure. This method gives the possibility to estimate a cost-effectiveness ratio of the studied surgical methods (ICER) and consequently in the future to compare the results with other treatments with calculated QALYs and ICERs. This should be useful in decision-making about different treatment methods in an economically constrained health care system.

Robotic hysterectomy in low-risk endometrial cancer was more expensive, mainly due to the procedure cost including the acquisition and maintenance of the robotic system and the cost for the robotic instruments. This has also been demonstrated previously by others (Tandogdu, et al. 2015, Iavazzo and Gkegkes 2017, Kristensen, et al. 2017). A contributing factor to these high costs could be the absence of competition in the market of robotic equipment.

Despite the significant differences in total operating theatre time, anaesthesia and surgery time in favour of abdominal hysterectomy, these were not the most important cost drivers in our study. Experienced staff in the operating theatre for robotic surgery could, to a lesser but not decisive extent, compensate for some of the robotic procedure cost as long as total time in the operating theatre, anaesthesia and surgery time were not comparable with the open procedure. This is also emphasised by Pellegrino et al. (Pellegrino, et al. 2016).
Table 13. Total mean cost per patient (in SEK) based on the study population of 25 robotic and 24 abdominal hysterectomies extrapolated to an annual caseload of 300 and 500.

|                      | Robotic hysterectomy | Abdominal hysterectomy | Difference in costs (RH-AH) 300 procedures | Difference in costs (RH-AH) 500 procedures |
|----------------------|----------------------|------------------------|-------------------------------------------|-------------------------------------------|
|                      | Based on 300 procedures annually | Based on 500 procedures annually | Based on 300 procedures annually | Based on 500 procedures annually |
| **Direct costs**     |                      |                        |                                          |                                           |
| Operation excl. instruments and robot | 17,562               | 15,293                 | 2,269                                    | 2,269                                    |
| Instruments          | 15,080               | 5,503                  | 9,570                                    | 9,574                                    |
| Da Vinci® robot Si   | 9,657                | -                      | 9,657                                    | 5,794                                    |
| Post anaesthesia care unit | 2,399              | 2,399                  | 0                                        | 0                                        |
| Care in gynaecological ward | 20,405              | 19,635                 | 770                                      | 770                                      |
| Readmissions with 24 h hospital stay | 0                  | 1,155                  | -1,155                                   | -1,155                                   |
| Unplanned outpatient visits to physician | 361                | 1,503                  | -1,142                                   | -1,142                                   |
| Unplanned outpatient visits to nurse | 264                | 1,281                  | -1,017                                   | -1,017                                   |
| **Total direct costs** | **65,728**           | **46,769**             | **18,952**                               | **15,093**                               |
| **Indirect costs**   |                      |                        |                                          |                                           |
| Sick leave           | 12,264               | 17,821                 | -5,557                                   | -5,557                                   |
| Informal care       | 187                  | 497                    | -310                                     | -310                                     |
| **Total indirect costs** | **12,451**          | **18,318**             | **-5,867**                               | **-5,867**                               |
| **TOTAL COSTS (direct + indirect)** | **78,179**          | **65,094**             | **13,085**                               | **9,226**                                |

Round figures are used for the convenience of the reader.
Exchange rate per December 31, 2018: US $ 100 = SEK 869.21; € 100 = SEK 1,025.67
The main advantages of the robotic surgery for the patient seem to be a shorter length of hospital stay, faster recovery and return to work, and fewer postoperative complications, besides the technical and ergonomic advantages for the surgeon.

We failed to demonstrate a shorter length of hospital stay after robotic hysterectomy compared with abdominal in early endometrial cancer as shown in other trials (Liu, et al. 2014, Herling, et al. 2016b, Park, et al. 2016, Kristensen, et al. 2017). However, these studies were not conducted in an ERAS programme. Economically, a shorter length of stay is a prerequisite to compensate for the high robotic procedure costs to make the procedure acceptable. By using an ERAS programme with standardised discharge criteria and by treating both groups similarly we were able to demonstrate the actual short and similar length of hospital stay in both groups from time of arrival in the operating theatre to discharge from the ward. In accordance with our findings, a recently published Danish study investigating the long-term resource consequences of introducing robotic surgery for treatment of early endometrial cancer, could not demonstrate a significant difference in days of hospitalisation when adjusting for time trends (Korsholm, et al. 2019). The robotic surgery generated additional costs, and no long term cost savings.

Sick leave did not differ significantly between the groups in our study, although the women in the abdominal group needed on average six days more sick leave, with the possibility of a not insignificant influence on costs. Productivity loss plays a key role in indirect costs. In prostate cancer the costs for sick leave following robotic surgery seemed to counterbalance the costs for the robotic procedure (Forsmark, et al. 2018). The societal costs for sick leave, as well as informal care, with low costs in both groups in our trial, have not previously been studied in cost-analyses in gynaecological cancer surgery.

Another important factor that could compensate economically for the high robotic costs is the higher incidence of complications following abdominal surgery. Several authors emphasised these post-discharge costs (Lau, et al. 2012, Leitao, et al. 2014). They argued that the greatest effect of cost neutralisation will be among hospitals with high laparotomy rates for endometrial cancer leading to higher hospital costs caused by postoperative complications following abdominal surgery. In our study, the high robotic procedure cost could only to a lesser extent be counterbalanced by the hospital cost for complications in the abdominal hysterectomy group. Maybe the magnitude of the abdominal surgery, both concerning the skin incision as low transverse and the intra-abdominal surgery, influences this. Also, the use of an ERAS programme in our study should be helpful in the prevention of postoperative complications (Wijk, et al. 2019).

The gain in QALY was low for the individual woman due to the short time horizon the effect of the robotic intervention lasted. The calculated cost per QALY gained in the robotic group is considered as very high by the Swedish society (Neumann, et al. 2017). Unfortunately the clinical benefits of the robotic procedure are economically converted into profits for the manufacturer and not for the society. More efforts should be made to prevent postoperative complications if the abdominal procedure should be an alternative treatment modality to minimally invasive surgery for endometrial cancer patients.
General Discussion

Methodological considerations

**RCT**

A blinded multicentre RCT is considered the gold standard for study design in clinically testing new treatments, drugs and surgical procedures leading to the most reliable form of scientific evidence, i.e. evidence of the highest grade. Results from several RCTs may be combined in systematic reviews being used in the conduct of evidence-based practice. Table 14 shows grades of evidence to assess an RCT.

**Table 14. GRADE, different levels of evidence.**

| GRADE               | Description                                                                 |
|---------------------|-----------------------------------------------------------------------------|
| High quality        | Further research is very unlikely to chance our confidence in the estimate of effect. |
| Moderate quality    | Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. |
| Low quality         | Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. |
| Very low quality    | We are very uncertain about the estimate.                                   |

Masking or blinding, traditionally single-, double or triple- is now, since the CONSORT 2010 Statement, defined as “blinded” or “unblinded” (open or open-label) with specification in the trial of who were blinded. The CONSORT 2010 Statement is an evidence-based, minimum set of recommendations for reporting RCTs. For the reports on our trials we followed these guidelines.

Blinding reduces or eliminates sources of experimental bias. In the Cyklokapron study, patients, caregivers and researchers were blinded. For obvious reasons patients and caregivers in the Robothyst study, a parallel group comparison on surgical treatment methods, could not be blinded. However, the laboratory personnel analysing the blood samples for tissue damage and inflammatory markers were blinded for the associated treatment modality.

The benefits of a multicentre study include a larger number of participants and the ability to compare results among centres, which increase the generalisability of the trial. The fact that gynaecological oncology surgeons performed all the operations in the Cyklokapron study may limit the generalisation of the results to other settings. The multicentre approach could also give biased results, for instance by the divergent treatment of blood loss in the various centres as a standardised blood transfusion protocol was lacking. We had no strictly defined criteria or protocol for when blood transfusions should be considered in patients following ovarian
cancer surgery who are exhibiting symptoms of anaemia. This may influence the rate of blood transfusion depending on the practice of each participating hospital, and implies a source of performance bias. Further on, the Cyklokapron study protocol allowed supplemental tranexamic acid and desmopressin if the surgeon observed unacceptable intraoperative bleeding with the possibility of performance bias. In the single centre Robothyst study the generalisability of the robotic hysterectomy towards other patient groups could be discussed as the study population only comprised women with early endometrial cancer. Due to a lack of facility resources, only one surgeon performed all the robotic operations. This could increase the risk of selection bias by trying to include appropriate patients for the robotic surgery. However, this risk is less likely as the patients were recruited consecutively and in each case the final appointment for the surgery was made after the woman had agreed to participate in the study.

Lack of homogeneity in the study population in the Cyklokapron study is a concern for the analysis. The women who entered the study had presumed or confirmed advanced ovarian cancer. Final diagnosis showed that not all had advanced ovarian malignancies and not all underwent extensive debulking radical surgery.

Randomisation prevents skewing or influencing the results by removing the element of choice both for the participant and the researcher. Random assignment by means of a computer programme removes selection and allocation bias or confounding. In the Cyklokapron study some baseline descriptive data were imbalanced statistically in spite of the randomisation procedure, with the risk of accidental bias; effect estimates can be confounded with the effects of these covariates. According to statistical considerations, 5% of such comparisons would be expected to be significant at the 5% level. In randomised trials any statistical differences in baseline characteristics between groups are, by definition, a result by chance (Altman and Dore 1990). In both trials we used a blocked randomisation process with blocks of ten and an allocation ratio of 1:1 to ensure good balance of patient characteristics in each group. The block size was unknown to the researchers in the Cyklokapron study but not in the Robothyst trial. Theoretically it was possible to guess the treatment method in each tenth patient in the Robothyst study. However, practically it is quite difficult to get an overview of the nine most recently included patients.

In both the Cyklokapron study and the Robothyst study, sample size determination with power calculation was carried out, affecting the RCT’s reliability in a positive way. In the Robothyst study, sample size estimation for the inflammatory markers was based on differences in CRP, resulting in a potential risk for insufficient powering of the other markers. However, our results did not support this.

**Estimation of blood loss**

Since accurate determination of blood loss is difficult, we used different models in the Cyklokapron study to estimate blood loss. All of these methods have shortcomings and should be used with caution in single cases. However, they are probably more reliable if analysed on a group level in randomised studies.
In Sweden, the intraoperative blood loss is usually estimated by the nurse anaesthetist. The blood volume in the suction device and the visual estimation of blood content in sponges and drapes is summed up. Sometimes the sponges are weighted. Because the estimation method can vary slightly between hospitals, there is a risk for interobserver variation. Estimation of postoperative blood loss is also complicated especially in the case of haematomas.

We found the haemoglobin dilution method or Hb-balance method described by Brecher (Brecher, et al. 1997) most appropriate for determining blood loss caused by extensive surgery. The method is based on the assumption that the state of normovolemia is re-established on the fifth day following surgery. An Hb blood sample on this day is related to the value preoperatively and the calculated predicted blood volume of the patient. An advantage of this method is that blood loss during this perioperative period, as occurs for example with haematomas, can also be estimated. Because this is a mathematical model negative values can also be obtained, as shown in our study, especially when the state of normovolemia was not established or blood transfusions were given. Even when this method is appealing, the Hb-balance method seems too complicated for use in clinical daily practice. So even then, the nurse anaesthetist has to continue estimate bleeding volume as is usually done in clinical practice, and must be aware that the intraoperative bleeding volume is usually underestimated and is about twice the visually estimated bleeding volume during the operation (Brecher, et al. 1997).

Questionnaires

The EQ-5D-3L (originally the former EQ-5D) is a validated broad questionnaire that is easy to use and applicable to the adult population in a wide range of situations. The form creates an index facilitating the ranking of the individual health state and further calculation of QALY, which is important in health economic evaluations. The questionnaire has a simple design with only five questions, referring to five dimensions of health with three response levels per dimension, which can imply difficulties in detecting small changes in the health state. The valuation of health states or generating the reference value set linked to the answers in the questionnaire is much debated. Differences in observed utilities for moderate and severe health states were found to be associated with some demographic factors, including gender, education, proportion urban population, and national health care expenditure (Xie, et al. 2014). Most likely the results also differ when an experience-based or hypothetical valuation of health states is done by respondents from the general population (Aronsson, et al. 2015). Another concern is the interpretation of the quality-of-life weights beneath zero. How is it possible to interpret health states worse than death? In our study the EQ-5D index for both groups started at about 0.80 and never reached beneath zero. Since 2005 a new version of the EQ-5D with five levels of severity has been developed, the EQ-5D-5L in order to improve the instrument’s sensitivity to small changes (Janssen, et al. 2018).

The SF-36 includes eight health concepts representing the most frequently measured concepts in widely used health surveys and those most affected by disease and treatment (Ware and Sherbourne 1992). Some SF-36 scales have shown lesser precision than the original long-form that the SF-36 scales were constructed to reproduce (Ware, et al. 1995). However, the...
actual Short Form is more practical and rarely misses a noteworthy difference in physical or mental health state in group comparisons (Katz, et al. 1992). The SPSQ focusses repeatedly on the experience and intensity of several postoperative symptoms and thus may draw the patients’ attention to symptoms that otherwise would not be noticed, resulting in an overestimation of perceived symptoms. However, according to earlier published data about fast track abdominal hysterectomy using the SPSQ (Wodlin, et al. 2011a), 95% of the patients in the trial reported the questions as “appropriate, giving a true picture of their experiences”.

**Surgical procedures and ERAS**

Robot-assisted laparoscopic surgery was introduced in gynaecological surgery in our department in 2010. An issue with relatively newly introduced surgical techniques is the learning curve for the procedure, which we thought had already been overcome for the robotic surgery but was still clearly demonstrated in our study between 2012 and 2016. The abdominal procedure was performed by six surgeons working at that time. All operations were conducted or supervised by accredited gynaecological oncologists. There is a risk of inaccuracy when several surgeons are performing the studied surgery, although this also gives a broader view and more accurately reflects the daily common practice.

ERAS has been well established since 2007 in our department so it was obvious to perform the study with standardised anaesthesia, preoperative intrathecal morphine in both groups, and the same care on the ward with standardised discharge criteria to keep other perioperative factors besides the surgery equal in the groups. This is particularly important when a risk for surgeon bias towards a new technique can be expected.

**Markers of tissue damage and inflammation**

The laboratory analyses of the seven selected markers showed levels and changes over time for all of the markers. However, IL-6 was below the level of detection one week preoperatively and six weeks postoperatively in nearly 43% of all women, and on the day of surgery before the operation and one week postoperatively in nearly 29% of all study participants. The question arises of why this IL-6 marker was not detectable on these different occasions of measurement. Was this related to the laboratory technique being not sufficiently sensitive or was the actual IL-6 level not elevated at all because of the low degree of inflammation or tissue damage? The latter seems a plausible explanation though only small amounts of IL-6 in pg/ml can be detected in healthy humans, and in nearly all pathophysiological states IL-6 is substantial elevated (Wolf, et al. 2014). This is consistent with our findings of a significant difference between the groups with briefly lower IL-6 levels two and 48 hours after robotic hysterectomy, reflecting a transiently lower inflammatory response following the robotic procedure compared with the abdominal procedure. Before and after this time period the IL-6 levels seemed normalised and very low, or not detectable.
Calculation of costs and QALY

Although data on clinical outcomes in the Robothyst study were collected prospectively the costs were estimated retrospectively. Cost accounting records and hospital prices derived from the year 2018 were used and personnel costs and costs due to sick leave were obtained from mean gross annual income for women in Sweden in 2018. This implies that the total costs are proportional and not the *de facto* costs between the treatment groups, which makes the cost comparison valid.

The small sample size could be seen as a limitation for the cost-effectiveness analysis. However, the sample size was powered for the primary outcome the EQ-5D index, which is crucial for the health economic evaluation because of the possibility to calculate QALY and costs, leading to the possibility of decision-making. QALY calculation enables future comparison with other treatments within and outside the field of gynaecological oncology when QALYs are more often used and expressed.

Long-term outcome including survival was beyond the field of this study, although for a health economic analysis the time horizon is an important factor. We assumed that the long-term outcome for both treatment groups was non-inferior according to earlier published trials on long-term oncologic safety following minimally invasive surgery in endometrial cancer (Koskas, et al. 2016, Lindfors, et al. 2018).
Conclusions

General conclusion

- The care of women with advanced ovarian cancer can be improved by using a single dose of tranexamic acid intravenously just before surgery, thereby decreasing bleeding volume and the need for blood transfusions with their negative consequences.

- The care of women with early stage endometrial cancer can be improved by using robot-assisted laparoscopic hysterectomy as a treatment method in an ERAS programme, resulting in a faster recovery of quality of life, less tissue damage and inflammation, and decreased stress response but at a substantially higher total cost for the society.

Specific conclusions

- A single dose of tranexamic acid given intravenously immediately before the operation reduced blood loss and the transfusion rate in surgery for advanced ovarian cancer.

- Robotic hysterectomy was associated with a faster postoperative recovery of the HRQoL compared with abdominal hysterectomy in an ERAS protocol treating low-risk endometrial cancer.

- Six weeks postoperatively, the HRQoL concerning the perception of general health was still rated higher in the robotic group without postoperative complications.

- Overall postoperative discomfort measured by the postoperative symptom sum score, pain, analgesic consumption and length of hospital stay was similar in the robotic and abdominal hysterectomy group.

- After discharge from the ward, postoperative symptoms were experienced to a higher extent by the women in the abdominal hysterectomy group.

- Complications following surgery for low-risk endometrial cancer influenced the HRQoL and length of hospital stay significantly.

- Robotic hysterectomy resulted in a fast transient lower inflammatory reaction, less tissue damage and a lower stress response compared with abdominal hysterectomy in an ERAS programme.
• Less tissue damage and inflammation in the robotic group could contribute to a faster recovery of the HRQoL.

• Robotic hysterectomy gained more QALYs compared with abdominal hysterectomy until six weeks after surgery, at a 20% higher total cost.

• The ICER or the cost to gain one QALY in treatment of low-risk endometrial cancer by robotic surgery was high compared with the abdominal operation.
Future perspectives

Perioperative care and surgical procedures in gynaecological oncology is a field needing continuous investigation to discover new treatment methods to improve the perioperative management of the patients, leading to faster recovery and hopefully also better prognosis, and in the ending giving a benefit for the society health-economically.

Further research is warranted to guide blood transfusion practices in patients with gynaecological malignancies. In this patient population blood transfusion is often given based on individual or local experience rather than evidence-based guidelines (Cybulska, et al. 2017). The indications for blood transfusion should be to improve tissue oxygen delivery, treat anaemia symptoms and consequently improve quality of life. The transfusion trigger for anaemia in gynaecological cancer is not defined and transfusion protocols are required. The link between transfusion, prognosis, and recurrence is worrying, and should lead to caution in surgeons’ decision-making on giving blood transfusions. High-level evidence that can be used to make effective recommendations is needed.

Another interesting field to study is the role of tranexamic acid on postoperative infections in patients undergoing gynaecological cancer surgery. Tranexamic acid works by blocking plasmin formation, resulting in the inhibition of fibrinolysis. Plasmin is known to stimulate inflammatory and immunosuppressive mediators. This plasmin-mediated immunosuppression in patients undergoing surgery can be directly reversed by tranexamic acid, thereby decreasing the postoperative infection rate, independent of the effect of reducing blood loss. Recent data in cardiac surgery indicates that tranexamic acid modulates the immune response and reduces the postsurgical infection rates, despite the administration of prophylactic antibiotics (Draxler, et al. 2019). Patients with diabetes seem to be refractory to the effect of tranexamic acid concerning postoperative infections and partially refractory to tranexamic acid treatment. In our Cyklokapron study we found that 20% of those in the tranexamic acid group and 32% of those in the placebo group had postoperative infections following radical debulking surgery for presumed advanced ovarian cancer, although not reaching statistical significance. The distribution of diabetes was statistically equal in the groups with 6 % in the tranexamic and 14% in the placebo group.

Robotic surgery in gynaecological oncology remains to be investigated in high-quality trials and in ERAS programmes, especially concerning long-term clinical outcomes and overall quality of life, using well-validated instruments applied in a standardised manner. Cancer recurrence and disease-free survival are issues that still need to be further explored before the expensive robotic technique can be fully accepted, even if laparoscopic and some robotic evidence does not show any difference in oncologic safety in endometrial cancer (Koskas, et al. 2016, Lindfors, et al. 2018). Recently, a randomised trial started called “Robot-assisted approach to cervical cancer (RACC)”, an international multicentre open-label study between robotic and abdominal radical hysterectomy with pelvic lymphadenectomy for woman with
cervical cancer, studying the five-year recurrence-free survival, postoperative complications and patient-reported outcomes (Falconer, et al. 2019).

Further investigation is needed in abdominal gynaecological cancer surgery with the aim of refining the surgical technique and preventing or decreasing postoperative complications associated with the specific procedure. This is important not only for ovarian cancer surgery as it progresses towards more extensive radical surgery with a high perioperative complication rate, but also for cervical cancer, where surgical treatment is shifting towards open surgery based on reports of decreased survival with minimally invasive surgery (Ramirez, et al. 2018). Further development of the ERAS programmes and the consistent use of these models are important steps towards achieving these goals (Wijk, et al. 2019).
Populärvetenskaplig sammanfattning

Kvalitetsförbättring av gynekologisk onkologisk kirurgi

Gynekologisk tumörkirurgi är ett viktigt område inom den gynekologiska onkologin. Kirurgin påverkar patientens livskvalitet, särskilt i det omedelbara förfallet efter operationen och har även stor betydelse för sjukdomsprognosen på längre sikt. Därför finns ett behov att ständigt söka medicinska och kirurgiska förbättringar för att därigenom förbättra livskvalitet och prognos för patienten. Denna avhandling baseras på två randomiserade kontrollerade studier:

1. "Kan tranexamsyra (Cyklokapron®) givet som en engångsdos strax före operationen minska blodförlusten och blodtransfusionsbehovet vid operation för misstänkt äggstockscancer?" ("Cyklokapronstudien")
2. "Ger laparoskopisk robotassisterad borttagnings av livmodern vid livmodern cancer mindre kroppslig påverkan och en snabbare återhämtning än konventionell borttagnings av livmodern genom ett bukväggsnitt?" ("Robothyststudien").

Studierna har till syfte att leda till medicinska och kirurgiska förbättringar inom den gynekologiska tumörkirurgin.

Optimal tumörkirurgi vid avancerad äggstockscancer innebär att tumörbördan makroskopiskt radikalt tas bort. Denna typ av kirurgi är tekniskt både krävande och omfattande, vilket därför ofta medför en betydande blödning under operationen. Enligt internationella studier uppgår blödningen vid operation för avancerad äggstockscancer till ungefär 1 liter och för att ersätta blodförlusten får upp emot 40 % av patienterna blodtransfusion.

Transfusioner av blodprodukter kan medföra allergiska reaktioner, bildning av antikroppar och ger en ökad risk för infektioner efter en operation. Blodtransfusion vid en canceroperation utgör också en riskfaktor för återfall i cancersjukdomen på grund av påverkan på immunsystemet. Detta sker oberoende om det är patientens eget blod eller blod från en blodgivare som ges. Det är därför angeläget att hitta sätt att undvika blodtransfusion.

Tranexamsyra motverkar upplösningen av blodkoagler genom att förhindra att plasminogen omvandlas till plasmin. Plasmin bidrar i vanliga fall till upplösningen av fibrin, det vill säga av ett koagel som bildas vid blödning. Läkemedlet har använts sedan minst 50 år tillbaka i Sverige vid blödningsproblem inom bland annat kvinnosjukvården. Någon systematisk användning vid gynekologiska bukingrepp finns inte beskriven i litteraturen. I studier har inte framkommit belägg för att blodprop skulle vara vanligare eller allvarligare hos patienter som får medlet och det verkar inte heller finnas en ökad frekvens av övriga komplikationer. Förutom medicinska skäl att minska blodförlusten och transfusion i samband med operation finns även ekonomiska skäl. En enhet blodkoncentrat är betydligt dyrare än en normaldos tranexamsyra.

Återhämtningen efter en större operation påverkas av många faktorer. Man kan förbättra och förkorta återhämtningen efter kirurgiska ingrepp genom att använda ett så kallad Enhanced Recovery After Surgery (ERAS) protokoll. Principerna för ERAS omfattar noggrann information inför ingreppet - om själva operationen och förfallet - optimering av narkos och smärtlindring, minimal användning av morfinliknande läkemedel, förebyggande av
illamående och kräkningar, tidig mobilisering och snabb återgång till normalt födointag efter operationen. Med detta förfarande har man kunnat minska vårdtiden på sjukhuset efter diverse bukoperationer med bibehållen medicinsk säkerhet och minskad förekomst av komplikationer efter ingreppet. 

Omfattningen av vävnadsskada som patienten utsätts för vid ett kirurgiskt ingrepp påverkar troligen återhämtningen. Vävnadsskada kan uttryckas och mätas genom förändringar i blodet av inflammatoriska och immunologiska celler, proteiner och stresshormon. Flera studier har visat att borttagning av livmoder med tittthålsteknik ger en mindre vävnadsskada än ingrepp som har gjorts genom ett buksnitt. Om denna mindre vävnadskada leder till en snabbare återhämtning är inte fastställt. Det är inte heller fastställt om användning av ett ERAS program med användning av ryggbedövning före operationen tillsammans med den allmänna narkosen påverkar förekomsten av inflammation, vävnadsskademarker och stresshormon i blodet.

Utvecklingen och introduktionen av en operationsrobot genomfördes i syfte att förbättra och förfina den kirurgiska tekniken och åstadkomma en snabbare återhämtning för patienten. Det har publicerats många studier inom gynekologisk robotassisterad kirurgi, men dessa studier är oftast av vetenskaplig låg kvalitet där man t.ex. beskriver hur man kan utföra metoden och hur säker den är. Det råder brist på randomiserade studier och särskilt studier där man använder ERAS program.

Syftet med ”Cyklokapronstudien” var att fastställa om man genom användning av tranexamsyra givet intravenöst som engångsdos omedelbart före operationen för misstänkt utbredd äggstockscancer kan minska blödningen i samband med ingreppet och transfusionsbehovet. 

Syftet med ”Robothyststudien” var att fastställa om man i ett ERAS program genom användning av robotkirurgi för borttagande av livmoder vid livmodercancer får en mindre vävnadsskada och en snabbare fysisk och psykisk återhämtning jämfört med borttagande av livmodern genom ett buksnitt och att undersöka om denna operationsmetod är kostnadseffektiv.

I Cyklokapronstudien, som pågick mellan mars 2008 och maj 2012, deltog fyra kvinokliniker, två universitetssjukhus (Linköping, Örebro) och två länssjukhus (Kalmar, Jönköping). Hundra kvinnor med misstänkt äggstockscancer planerade för operation inkluderades. Femtio kvinnor fick tranexamsyra och 50 fick ett läkemedel utan aktiv substans, vanligt koksalt, utan att veta vilket läkemedel man hade fått. Resultaten visade att den totala blodförlusten var lägre i tranexamsyra gruppen (520 ml) jämfört med gruppen som inte hade fått läkemedlet (730 ml) och behovet av blodtransfusion visade sig vara 30 % i tranexamsyra gruppen och 44 % i gruppen som inte hade fått det aktiva läkemedlet.

I Robothyststudien deltog kvinnor med tidig livmodercancer planerade för operation på Kvinnokliniken, Universitetssjukhuset i Linköping mellan februari 2012 och maj 2016. Totalt 50 kvinnor inkluderades, 25 fick en laparoskopisk robotassisterad borttagning av livmodern
och 25 en operation genom ett buksnitt, ett lågt tvärsnitt, s.k. bikinisnitt. Studien följde ett ERAS program och alla deltagare fick före den vanliga sövningen också en ryggbedövning. Resultaten visade att kvinnor i robotgruppen återhämtade sig 2 veckor snabbare än kvinnor opererade via ett buksnitt vad gäller livskvalitet, mätt med livskvalitetsformuläret EQ-5D-3L. Hälso- och vagnrelaterad livskvalitet mätt med livskvalitetsformuläret SF-36 sex veckor efter operationen visade att alla var återhämtade men med en bättre livskvalitet för robotgruppen vad gäller allmän hälsa och social funktion. Komplikationer påverkade livskvaliteten negativt i bägge grupperna. Generellt obehag direkt efter operationen, smärta, behov av smärtlindring och vårdtid var lika för båda grupperna. Resultaten visade också att vävnadskadan, inflammationen och stressreaktionen i samband med operationen var lägre i gruppen som gick igenom en robotassisterad laparoskopisk borttagning av livmodern jämfört med operationen genom ett bikinisnitt. Hälsoekonomisk analys av bägge operationsmetoderna för behandling av kvinnor med tidig livmodercancer i ett ERAS program visade att robotassisterad laparoskopisk borttagande av livmodern är effektivt med en snabbare återhämtning men till en betydligt högre kostnad. Det totala priset för en robotassisterad operation var 20 % högre jämfört med operationen genom ett bikinisnitt.

Sammanfattningsvis kan vården för kvinnor med äggstockscancer förbättras genom att använda tranexamsyra vid operation för misstänkt äggstockscancer, så att blodförlust och transfusionsbehovet med dess negativa följder kan minskas. Vården av kvinnor med tidig livmodercancer kan förbättras genom att använda en robotassisterad laparoskopisk operation för borttagning av livmodern med en mindre vävnadsskada och påverkan på immunsystemet samt snabbare återhämtning i livskvalitet, men till en påtagligt högre kostnad för samhället.
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Appendix

Appendix 1 FIGO ovarian cancer staging system 2014

| Stage | Findings |
|-------|----------|
| I     | Tumour confined to ovaries. |
| IA    | Tumour limited to one ovary (capsule intact), no tumour on ovarian surface, no malignancy cells in the ascites or peritoneal washings. |
| IB    | Tumour limited to both ovaries (capsule intact), no tumour on ovarian surface, no malignancy cells in the ascites or peritoneal washings. |
| IC    | Tumour limited to one or both ovaries with any of the following: surgical spill intraoperatively, capsule rupture before surgery or tumour on ovarian surface, or malignancy cells present in the ascites or peritoneal washings. |
| II    | Tumour involves one or both ovaries with pelvic extension. |
| IIA   | Extension and/or implants on the uterus and/or fallopian tubes. |
| IIB   | Extension to other pelvic intraperitoneal tissues. |
| III   | Tumour involves one or both ovaries with cytological or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal nodes. |
| IIIA  | Metastasis to the retroperitoneal lymph nodes with or without microscopic peritoneal involvement beyond the pelvis. |
| IIIB  | Macroscopic peritoneal metastases beyond the pelvic brim ≤ 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes. |
| IIIC  | Macroscopic peritoneal metastases beyond the pelvic brim >2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes. |
| IV    | Distant metastasis excluding peritoneal metastases. |
| IVA   | Pleural effusion with positive cytology. |
| IVB   | Metastases to extra-abdominal organs or parenchymal metastases. |
**Appendix 2 EQ-5D-3L**

**Hälsoenkät - EQ-5D**  

**Ifylles (tidpunkt)**

Markera, genom att kryssa i en ruta i varje nedanstående grupp, vilket påstående som bäst beskriver Ditt hälsotillstånd idag. Var vänlig fyll i vid samma tidpunkt varje dag.

Datum för ifyllande: _______________________

**Rörlighet**

1. Jag går utan svårigheter
2. Jag kan gå men med viss svårighet
3. Jag är sängliggande

**Hygien**

1. Jag behöver ingen hjälp med min dagliga hygien, mat eller påklädning
2. Jag har vissa problem att tvätta eller klä mig själv
3. Jag kan inte tvätta eller klä mig själv

**Huvudsakliga aktiviteter**  
(t ex arbete, studier, hushållssysslor, familje- och fritidsaktiviteter)

1. Jag klarar av min huvudsakliga sysselsättning
2. Jag har vissa problem med att klara av min huvudsakliga sysselsättning
3. Jag klarar inte av min huvudsakliga sysselsättning

**Smärtor/besvär**

1. Jag har varken smärtor eller besvär
2. Jag har måttliga smärtor eller besvär
3. Jag har svåra smärtor eller besvär

**Rädsla/nedstämdhet**

1. Jag är inte orolig eller nedstämd
2. Jag är orolig eller nedstämd i viss utsträckning
3. Jag är i högsta grad orolig eller nedstämd
Papers

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On Quality Improvement in Gynaecological Cancer Surgery

with emphasis on perioperative outcome, recovery and health economics

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