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MINNA MÄENPÄÄ

Robotic-assisted Laparoscopic Surgery in Gynecologic Oncology

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ACADEMIC DISSERTATION
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UNIVERSITY OF TAMPERE

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University of Tampere, Faculty of Medicine and Life Sciences
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Finland

Supervised by
Professor Johanna Mäenpää
University of Tampere
Finland
Docent Kari Nieminen
University of Tampere
Finland

Reviewed by
Docent Maarit Anttila
University of Eastern Finland
Finland
Docent Mikko Loukovaara
University of Helsinki
Finland

Cover design by
Mikko Reinikka

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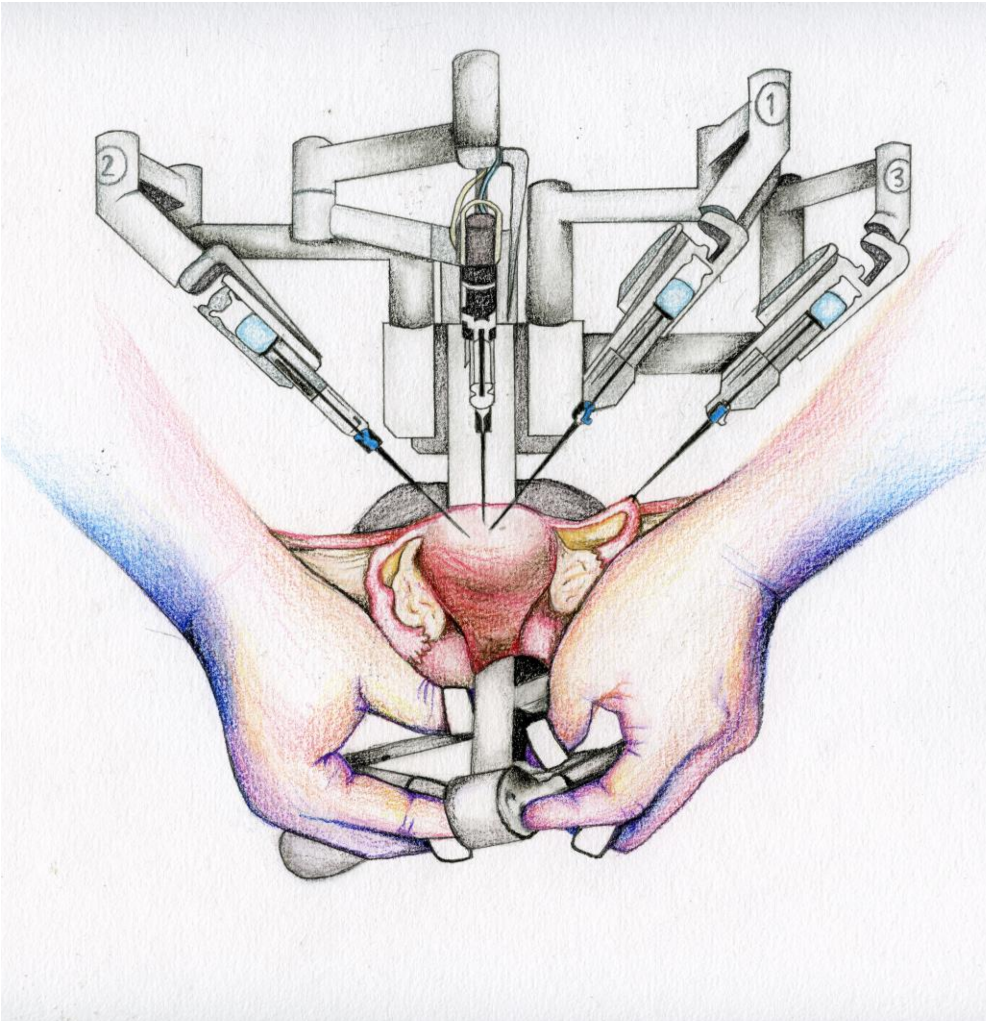

To my Parents and to Miko, Pinja and Kiira

ABSTRACT

Robotic-assisted gynecological laparoscopic surgery was approved for medical use by FDA in 2005, and has fast become more widely used globally since then. In Finland, it was taken into use in December 2008 in urology, and the first gynecological robotic-assisted surgery in Finland was performed on 24 March 2009 at Tampere University Hospital. Over the following eight years, 700 gynecological operations have been performed at Tampere University Hospital by aid of the robot, mostly because of gynecological cancers. Robotic-assisted surgery is especially well suited for the treatment of endometrial and cervical cancer as well as the treatment of early-stage ovarian cancer. Out of these, high-risk endometrial cancer is an especially significant target group.

The aim of the study was to explore how successful the implementation of robotic-assisted technique has been at the Department of Obstetrics and Gynecology. The learning of robotic-assisted operations was studied with learning curves. Successful robotic-assisted surgeries and their outcomes were reviewed both retrospectively and prospectively. Robotic-assisted laparoscopic surgery was compared with traditional laparoscopic surgery in a randomized prospective study in patients with endometrial cancer, and the costs of both surgical techniques were calculated.

The first retrospective study consisted of the first 300 robotic-assisted laparoscopic surgeries in chronological order. Out of these, 81% were performed due to gynecological cancer and 19% due to benign indications. Robotic-assisted surgery was found to be a safe and effective way to operate on gynecological diseases. Robot technology was implemented efficiently by a well-trained robotic team consisting of gynecologists, operating room nurses (both instrument and anesthetic nurses) and anesthesiologists. Motivated personnel quickly learned the special characteristics of the robotic-assisted surgical technique. In operations for endometrial cancer, the learning curve for robotic-assisted surgery was short, approximately 10 operations. In addition to shortening of the operation time, more lymph nodes were removed after the learning curve. Preparation of the operating room was also found to be faster, and operating room time shortened significantly already after the first months.

A randomized, prospective study was started after the learning curve was established, at the end of 2010, and material was collected until the fall of 2013. The primary aim of the study was to find out if a robotic-assisted operation was slower to perform than a traditional operation, like earlier non-randomized studies had suggested. 101 patients with endometrial cancer scheduled for surgery were randomized into two groups: robotic-assisted and traditional laparoscopic operation. The randomization was allocated by age and weight between the groups, making background factors of the two groups as similar as possible. The median operation time was 139 min (range 86–197 min) in the robotic group (n=50) and 170 min (range 126–259 min) in the traditional laparoscopy group (n=49) ($p<0.001$). No conversions to open surgery were made in the robotic group but there were five conversions in the traditional group. In the robotic group, there were fewer intraoperative complications and more postoperative complications.

Another aim of the study was to find out the cost of surgery in patients with endometrial cancer, both in the robotic-assisted group and the traditional laparoscopy group in the framework of the randomized trial. The costs of both surgical techniques and complications during the 6-month follow-up period were examined. Total costs of surgical treatment were EUR 1,928 higher in the robotic-assisted group (median costs of traditional laparoscopy EUR 5,487, vs. median costs in robotic-assisted laparoscopy, EUR 7,415, $p<0.001$). The cost difference is mainly explained by more expensive instruments and devices used in robotic-assisted surgery as well as more expensive operating room and recovery room times.

Removal of lymph nodes plays an important role in the surgery of patients with gynecological cancer. One aim of the study was to explore how lymphadenectomies succeed when using the robot-assisted technique. In the randomized study, no significant difference was found in the number of lymph nodes removed in pelvic lymphadenectomy between the robotic-assisted and the traditional laparoscopy group, 25 (range 14–52) vs. 23 (range 11–50) $p=0.273$, respectively. The success rate of para-aortic lymphadenectomy using the robotic-assisted technique was studied using 7-year retrospective material on patients with gynecological cancer. Para-aortic lymphadenectomy succeeded in 83% (235/283) of operations to a high level; the area below the left renal vein and above the inferior mesenteric artery (IMA). 22% of both all patients (61/283) and of patients with endometrial cancer (38/175) had metastases in lymph nodes. In patients with high risk endometrial cancer, the rate of especially para-aortic lymph node metastases was relatively high, 15% in total, and 6% had only para-aortic metastases. The number of removed lymph nodes increased in the para-aortic area as the surgeon performed more operations, and a learning curve was evident. There was a significant difference (p=0.004) between the first 10 (median 11.5 lymph nodes, range 0–26) and last 10 operations (median 18, range 1–35).

In conclusion, robotic-assisted laparoscopic surgery is very suitable for the surgical treatment of patients with gynecological cancer. Relatively high costs can be balanced against successful challenging operations. Implementation of robotic-assisted surgery has been smooth, and operations have been effective and safe to perform.

TIIVISTELMÄ

FDA hyväksyi robottiavusteisen laparoskooppisen leikkaustekniikan gynekologiseen käyttöön vuonna 2005, ja tämän jälkeen sen käyttö on levinnyt nopeasti ja maailmanlaajuisesti. Suomessa se otettiin käyttöön joulukuussa 2008 urologisissa leikkauksissa, ja Suomen ensimmäinen gynekologinen robottiavusteinen leikkaus tehtiin 24.3.2009 Tampereen yliopistollisessa sairaalassa (Tays). Seuraavan kahdeksan vuoden aikana Taysissa on tehty robotin avulla 700 gynekologista leikkausta, joista suurin osa gynekologisten syöpien vuoksi. Robottiavusteinen leikkaus sopii erityisen hyvin kohdunrunkosyövän, kohdunkaulan syövän ja alkuvaiheen munasarjasyövän hoitoon. Näistä korkean riskin kohdunrunkosyövän leikkaushoito on merkittävin kohderyhmä.

Tutkimuksen tarkoituksena oli selvittää robottiavusteisen kirurgian käyttöönoton sujuvuutta ja soveltuvuutta gynekologisessa kirurgiassa. Leikkaustekniikan oppimista selvitettiin oppimiskäyrien avulla. Robottileikkauksien onnistumista ja tuloksia selvitettiin sekä retrospektiivisesti että prospektiivisesti. Robotti-avusteista laparoskooppista leikkausta verrattiin satunnaistetussa etenevässä tutkimuksessa perinteiseen laparoskooppiseen leikkaukseen kohdunrunkosyöpäpotilailla, ja leikkaustapojen kustannukset selvitettiin.

Ensimmäinen retrospektiivinen työ käsitti 300 ensimmäistä robottiavusteista laparoskooppista leikkausta. Näistä 81% tehtiin gynekologisen syövän vuoksi ja 19% hyvänlaatuisten syiden vuoksi. Robottiavusteinen kirurgia todettiin turvalliseksi ja tehokkaaksi leikkaustavaksi gynekologisessa kirurgiassa. Robottiavusteisen tekniikan käyttöönotto onnistui sujuvasti hyvin koulutetulta robottitiimiltä, johon kuuluivat gynekologit, leikkausalihoitajat (sekä instrumentti- että anestesiahoitajat) ja anestesialääkärit. Motivoitunut henkilökunta oppi nopeasti robottileikkaustekniikan erityspiirteet. Kohdunrunkosyövän leikkauksissa todettiin robottileikkausten oppimiskäyrän olevan lyhyt, noin. 10 leikkausta. Sen lisäksi, että leikkausaika lyheni, myös imusolmukkeita poistettiin enemmän oppimiskäyrän jälkeen. Leikkaussalivalmisteluissa todettiin niin ikään nopeutumista ja leikkaussaliaikaa saatiin lyhennettyä merkittävästi jo ensimmäisten kuukausien jälkeen.

Satunnaistettu, prospektiivinen tutkimus aloitettiin loppuvuodesta 2010 ja aineistoa kerättiin syksyyn 2013. Ensisijaisena tavoitteena oli selvittää, onko

robottiavusteinen leikkaus pitkäkestoisempi kuin perinteinen laparoskooppinen leikkaus, mihin aikaisempien satunnaistamattomien tutkimusten tulokset ovat viitanneet. 101 kohdunrunkosyöpäpotilasta satunnaistettiin kahteen ryhmään, joista toiselle tehtiin robottiavusteinen ja toiselle perinteinen laparoskooppinen leikkaus. Satunnaistaminen jyvitettiin iän ja painon suhteen, jolloin saatiin muodostettua kaksi taustatekijöiltään mahdollisimman samanlaista ryhmää. Kaksi potilasta jätettiin tutkimuksesta pois (laparoskopiaryhmä). Robottiryhmässä (n=50) leikkausajan mediaani oli 139 (vaihtelu 86-197) min. ja vastaavasti perinteisessä laparoskopiaryhmässä (n=49) 170 (vaihtelu 126-259) min. (p<0.001). Robottiavusteisessa ryhmässä ei ollut lainkaan konversioita avoleikkauksiksi, kun taas perinteisessä ryhmässä niitä oli viisi. Leikkauksen aikana tulleita komplikaatioita oli robottiryhmässä vähemmän, mutta leikkauksen jälkeen tulleita komplikaatioita oli enemmän.

Tutkimuksen toisena tarkoituksena oli selvittää satunnaistetun aineiston avulla robotti-avusteisen ja perinteisen laparoskopiaryhmän kustannukset kohdunrunkosyövän potilaiden hoidossa. Kustannuksissa otettiin huomioon sekä leikkaushoidon että puolen vuoden seurannan aikana ilmaantuneiden komplikaatioiden. Kokonaiskustannukset leikkaushoidon osalta olivat 1928 € korkeammat robottiryhmässä (mediaani 7415 € robotti-avusteiselle laparoskopialle ja 5487 € perinteiselle laparoskopialle, p<0.001). Kustannusten ero selittyi pääasiallisesti robottiavusteisen kirurgian kalliimmista instrumenteista ja laitteista sekä kalliimmasta leikkaussaliajasta ja heräämövalvonnasta.

Gynekologisten syöpäpotilaiden leikkaushoidossa imusolmukkeiden poistolla on merkittävä rooli. Yksi tutkimuksen tavoitteista oli selvittää, miten imusolmukkeiden poisto onnistuu robottiavusteisella tekniikalla. Satunnaistetussa työssä ei havaittu merkittävää eroa lantion alueelta poistettujen imusolmukkeiden määrässä robottiavusteisen ja perinteisen laparoskopiaryhmän välillä, koska niitä oli 25 robottiryhmässä (mediaani, vaihtelu 14-52) ja 23 (vaihtelu 11-50) perinteisessä ryhmässä (p=0.273). Para-aortaalialueen imusolmukkeiden poiston onnistumista robotti-avusteisella tekniikalla selvitettiin seitsemän vuoden retrospektiivisesti kerätystä gynekologisten syöpäpotilaiden aineistosta. Para-aortaalialueen imusolmukkeiden poisto onnistui 83%:ssa (235/283) leikkauksia korkealle tasolle; vasemman munuaislaskimon alapuolella ja IMA:n (a. mesenterica inferior) yläpuolella olevalle alueelle. Sekä koko aineistossa (61/283), että endometriumkarsinoomapotilailla (38/175) oli 22%:lla imusolmukkeissa syövän etäpesäkkeitä. Endometriumkarsinoomapotilailla erityisesti para-aortaalialueen imusolmuke-etäpesäkkeiden osuus oli suhteellisen korkea, 15%, ja kuudella prosentilla potilaista oli ainoastaan para-aortaalisia etäpesäkkeitä. Poistettujen imusolmukkeiden määrä lisääntyi para-aortaalialueella kirurgin leikkausmäärän lisääntyessä, ja oppimiskäyrä oli nähtävissä. Kymmenen ensimmäisen (mediaani 11.5, vaihtelu 0-26) ja kymmenen viimeisen (mediaani 18, vaihtelu 1-35) leikkauksen välinen ero oli tilastollisesti merkitsevä (p=0.004).

Robottiavusteinen laparoskooppinen leikkausmenetelmä näyttää soveltuvan hyvin gynekologisten syöpäpotilaiden leikkaushoitoon. Suhteellisen korkeiden kustannusten vastapainona on ollut vaativien leikkausten hyvä onnistuminen. Robottiavusteisen leikkaustekniikan käyttöönotto on ollut sujuvaa, ja robottileikkaukset ovat osoittautuneet tehokkaiksi ja turvallisiksi.

TABLE OF CONTENTS

LIST OF ORIGINAL COMMUNICATIONS

The present study is based on the following articles, which have been referred to in the text by their Roman numerals (I–IV):

I. Implementing robotic surgery to gynecologic oncology: the first 300 operations performed at a tertiary hospital. Mäenpää M, Nieminen K, Tomás E, Luukkaala T, Mäenpää JU. Acta Obstetricia et Gynecologica Scandinavica 2015 May;94(5):482-8.

II. Robotic-assisted vs traditional laparoscopic surgery for endometrial cancer: a randomized controlled trial. Mäenpää MM, Nieminen K, Tomás EI, Laurila M, Luukkaala TH, Mäenpää JU. American Journal of Obstetrics and Gynecology 2016 Nov;215:588.e1-7.

III. Costs of robotic-assisted versus traditional laparoscopy in endometrial cancer. Riikka-Liisa K. Vuorinen, Minna M. Mäenpää Kari Nieminen, Eija I. Tomás, Tiina H. Luukkaala, Anssi Auvinen, Johanna U. Mäenpää. International Journal of Gynecological Cancer 2017 Oct;27(8):1788–1793.

IV. Robotic-assisted infrarenal para-aortic lymphadenectomy in gynecological cancers: technique and surgical outcomes. Minna M. Mäenpää, Kari Nieminen, Eija I. Tomás, Tiina H. Luukkaala, Johanna U. Mäenpää. Submitted to International Journal of Gynecological Cancer on June 27th 2017.

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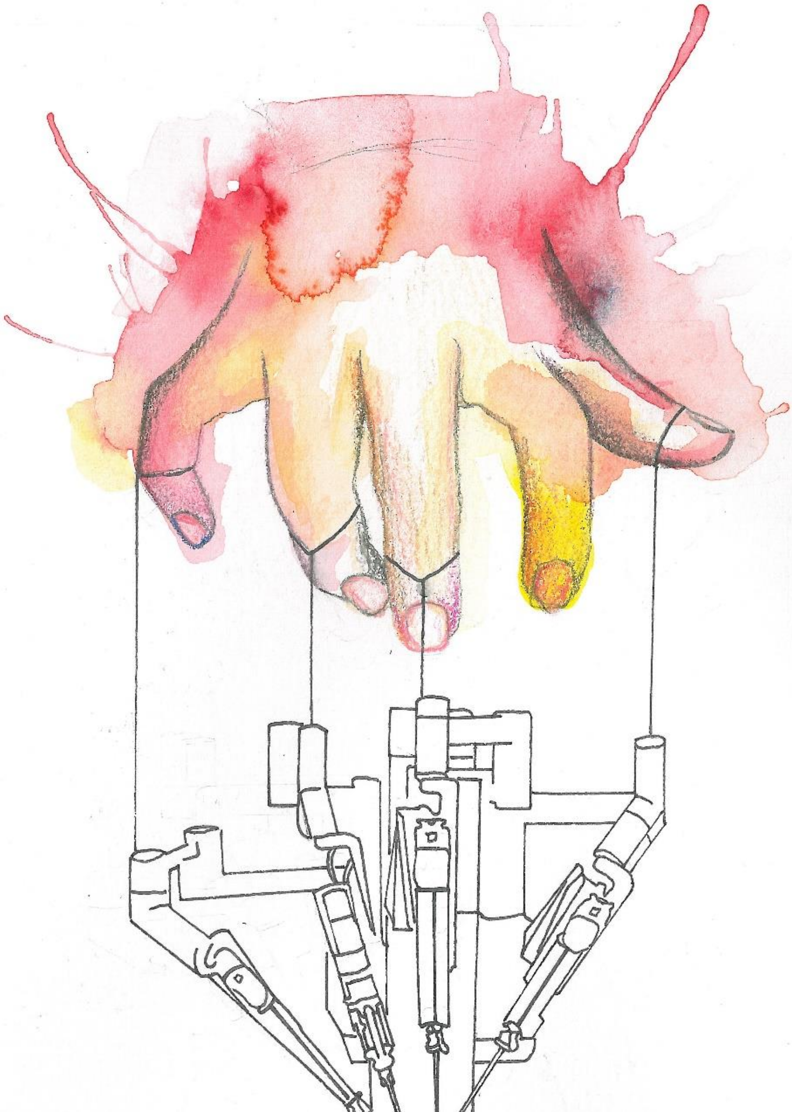
ABBREVIATIONS

3D	three-dimensional
BMI	body mass index
BSO	bilateral salpingo-ophorectomy
Ca 12-5	cancer antigen, carbohydrate 12-5
CO2	carbon dioxide
CT	computed tomography
DD	double docking
EBL	estimated blood loss
EUR	Euro
FDA	Food and Drug Administration
FIGO	International Federation of Gynecology and Obstetrics
GOG	Gynecologic Oncology Group
HE4	human epididymis protein 4
HGSC	high grade serous cancer
HPV	human papillomavirus
hr-HPV	high risk HPV
ICG	indocyanine green
IMA	inferior mesenteric artery
LH	laparoscopic hysterectomy
LVI	lymphovascular involvement
Md	median
MIS	mini-invasive technique
MRI	magnetic resonance imaging
n.d	no data
OR	operating room
ORH	open radical hysterectomy
OS	overall survival
PACU	post-anesthesia care unit
PALND	para-aortic lymphadenectomy/lymph node dissection
PET-CT	positron emission tomography

PFS	progression-free survival
PLND	pelvic lymphadenectomy/lymph node dissection
R0	residual 0 cm (optimal surgical outcome)
RRH	robotic-assisted radical hysterectomy
SD	single docking
SLN	sentinel lymph node
LRH	laparoscopic radical hysterectomy
US	ultrasound
USD	United States Dollar
VH	vaginal hysterectomy
vs.	versus



INTRODUCTION

Gynecological cancers include endometrial cancer, cervical cancer, ovarian cancer, fallopian tube cancer, chorion carcinoma, vaginal and vulvar cancers. Surgery is the basis for the treatment of gynecological cancers. Surgical treatment is not possible in exceptional cases, generally because the cancer has spread extensively. Gynecological cancers that are suitable for laparoscopic surgical technique include endometrial and cervical cancer as well as early-stage ovarian and fallopian tube cancer. In Finland and other developed countries, endometrial cancer is the most prevalent of these, and the cause for most laparoscopic oncologic/cancer operations. In 2012, 167,900 new cancers of the corpus uteri were diagnosed and it caused 34,700 deaths worldwide (Torre, Bray et al. 2015).

In endometrial cancer, the aim is always to remove at least the uterus, usually also the ovaries and fallopian tubes. Removal of lymph nodes, lymphadenectomy, is performed in the pelvic and para-aortic area in selected high-risk patients. The omentum is also removed in selected patients (Creasman 2009). In cervical cancer, the uterus is removed in a radical or standard manner based on the extent of the cancer. In radical fertility-sparing surgery, the uterine cervix and in most cases pelvic lymph nodes/sentinel node(s) are removed. If the uterus is to be removed, usually also the ovaries and fallopian tubes, and pelvic lymph nodes are removed (Oaknin, Rubio et al. 2015). In ovarian cancer, the aim is always to remove all tumors and to perform a staging operation where the omentum and pelvic and para-aortic lymph nodes are removed in addition to uterus and ovaries and fallopian tubes. Ovarian cancer is often diagnosed after it has spread, and its surgical treatment is generally an open surgery (Mutch, Prat 2014).

In gynecological surgery, there was a steep increase of laparoscopies at the end of the 1990s. This mini-invasive technique (MIS) was found to have distinct benefits: less intraoperative bleeding, shorter hospital stays and faster recovery. These benefits were particularly pronounced for elderly and possibly debilitated cancer patients (Kornblith, Huang et al. 2009). No difference in cancer prognosis has been found between the different surgical techniques, laparotomy and MIS, in endometrial carcinoma (Walker, Piedmonte et al. 2012) and in cervical carcinoma (Mendivil, Rettenmaier et al. 2016).

The next and newest development of mini-invasive technique was robotic-assisted technique. Robotic-assisted technique has distinct benefits over traditional endoscopic operations. The surgeon does not move endoscopic instruments in the abdominal cavity like in a traditional endoscopic operation. Instead, the surgeon uses console joysticks to move robotic arms. This way, all trembling of hands is filtered out, and tireless robot arms are easy to move with a flick of a wrist using the joysticks. When working in the console, the surgeon has an ergonomic operating position and a good three-dimensional (3D) view of the abdominal cavity (Lin, Wakabayashi et al. 2009, Oehler 2009).

The Da Vinci robot (da Vinci Surgical System, Intuitive Surgical Inc., Sunnyvale, CA) was taken into use in gynecological surgery in 2005. After that, the number of robotic-assisted operations has experienced strong global growth in gynecology (Mendivil, Holloway et al. 2009). This is despite the fact that there has been a lack of randomized studies comparing robotic-assisted and traditional gynecological laparoscopy, but on the other hand the high cost of robotic-assisted surgery has limited its implementation. In gynecology, robotic-assisted surgery is best suited to gynecologic oncologic operations that require demanding and precise working.

The aim of this study was to explore how robotic-assisted laparoscopic surgery has been implemented in Tampere. The study was conducted at Tampere University Hospital, where robotic-assisted surgery was first started and where the greatest number of robotic-assisted gynecological operations have been performed. The patients included in the study mostly have cancer, most of them endometrial cancer. One particular objective was to find out how robotic-assisted surgery differs from traditional laparoscopic surgery in patients with endometrial cancer and what is the cost difference between these two techniques. Another main objective was to study the learning process of the new technique, i.e. the learning curve of operations on patients with gynecological cancer; how successful lymphadenectomy, which has an important role in cancer operations, is when using robotic-assisted surgery, and what the entire learning process is like.

1 REVIEW OF THE LITERATURE

1.1 Endometrial cancer

Endometrial carcinoma is globally the sixth most common cancer in women, with 320,000 new cases annually, or 4.8% of cancers in women. The estimated age-standardized rates (ASRs, World standard) incidence is 8.3 per 100,000 women. The highest incidence rates are found in North America (19.1 per 100,000) and Northern and Western Europe (12.9–15.6 per 100,000), including Finland (13.2 per 100,000). The rates are low in South-Central Asia (2.7 per 100,000) and in the most parts of Africa (fewer than 5 per 100,000) (Ferlay, Soerjomataram et al. 2015).

In 2016 in the United States, the uterine corpus was found to be the fourth most common primary site of all new cancers, 60,050 (7%). It was preceded by breast, lung and colorectal cancers (Siegel, Miller et al. 2016). In developed countries, endometrial cancer is the most common gynecological cancer and its incidence is growing. In Finland, endometrial carcinoma was diagnosed in 836 women in 2014, compared 243 in 1953. In 2014 in Finland, the incidence rate was 13.2 per 100,000, and relative survival was 94% at 1 year and 84% at 5 years in cancers diagnosed in 2010–2014 (www.cancerregistry.fi). The average age at diagnosis is 63 years. Endometrial cancer causes symptoms, usually postmenopausal bleeding (90% of patients), which is why it is often diagnosed in the early stage and curative treatment is possible (Morice, Leary et al. 2016). In the United States, it caused 4% (10,470) of all cancer deaths (Siegel, Miller et al. 2016). In Finland, the rate was 3.2% (www.cancerregistry.fi).

In the United States (in 2005–2011), at the time of diagnosis the cancer was localized in 67% of cases, regional in 21% and metastatic in 8%. In a few cases (4%), the extent was not known (Siegel, Miller et al. 2016). In developed countries in general, endometrial cancer is often diagnosed (80%) at the FIGO Stage I and can thus be cured by surgery, albeit followed by adjuvant therapy if high-risk features are encountered (Colombo, Creutzberg et al. 2016).

The five-year relative survival rate in all stages of endometrial cancer is 82% (United States, 2005 to 2011). The five-year relative survival rate depends on the extent of the cancer, however. In localized cancer of the endometrium it is 95%, in regional cancer 68% and in metastatic cancer 17% (Siegel, Miller et al. 2016). Cancer advances within one year in most patients whose cancer has spread outside the uterus, when histology is more aggressive (Sutton, Axelrod et al. 2005, Fleming, Brunetto et al. 2004).

In endometrial carcinoma, staging classification is performed surgically. The International Federation of Gynecology and Obstetrics (FIGO) defined the first surgical classification in 1988 (Benedet, Pettersson 2003, Creasman 1990, Di Saia, Creasman 2012). Surgery forms the basis for the treatment of endometrial carcinoma. Traditionally, surgery has involved removal of the uterus, ovaries, fallopian tubes and pelvic lymph nodes as well as collection of cytological specimens. Knowledge on the subtypes and risk factors of endometrial carcinoma has made its surgical treatment more diverse and individualized. Advance in surgical care has led to a more mini-invasive surgical technique (Morice, Leary et al. 2016). Over the last 20 years, laparotomy has been replaced by minimally-invasive laparoscopic techniques, of which robotic-assisted surgery has lately become increasingly popular (Scalici, Laughlin et al. 2014).

During the last 5–10 years, treatment of endometrial carcinoma has become more complex. The histological classification of the cancer now has a bigger impact on the surgical treatment, adjuvant therapy and prognosis. Pelvic lymphadenectomy has been replaced with a recommendation of complete lymphadenectomy, which includes removal of para-aortic lymph nodes in addition to pelvic lymph nodes. On the other hand, guidelines have been created for situations where no lymphadenectomy has to be performed, and a large number of studies have been conducted on the removal of the sentinel node (Morice, Leary et al. 2016). Several studies have also been conducted on the necessity of adjuvant therapy, and the staging classification that describes the risk of cancer recurrence was amended in 2009 (Creasman 2009).

1.1.1 Risk factors

Obesity increases the risk of carcinoma. The risk of cancer increases 50% per every 5 units increase in BMI (Aune, Rosenblatt et al. 2015). The other known risk and protective factors of endometrial carcinoma are given in Table 1. (Von Gruenigen, Gil et al. 2005, Fader, Arriba et al. 2009, Sheikh, Althouse et al. 2014, Morice, Leary et al. 2016, Boronow, Morrow et al. 1984, Soini, Hurskainen et al. 2014, Lawrence, Lawrence et al. 1987, Felix, Yang et al. 2014, Di Saia, Creasman 2012)

Table 1. The risk and protective factors of endometrial carcinoma

Increase the risk	Decrease the risk
Obesity	Use of combined oral contraceptives
Anovulatory cycles	Use of progesterone in hormonal therapy
Exposure to endogenous and exogenous estrogens:	An intrauterine device that contains levonorgestrel
Early age of menarche	Smoking
Nulliparity	Parity
Late menopause	
Diabetes	
Over 55 years of age	
Use of tamoxifen	
Genetic mutations: Hereditary nonpolyposis colon cancer (HNPCC, Lynch syndrome)	

1.1.2 Endometrial cancer subtypes

Endometrial carcinoma consists of a heterogenic group of subtypes that are very divergent. The subtype and its characteristics have an effect on the treatment and prognosis of the cancer.

For 30 years, endometrial carcinomas have been divided into two main groups based on histology, degree of differentiation (grade) and the occurrence of hormone receptors. The most common subtype is low-grade, endometrioid, diploid, frequent microsatellite instability (40%), hormone-receptor-positive endometrial cancer, which has a good prognosis (overall survival 85% at 5 years). Type II endometrial cancers are described as non-endometrioid (serous, clear-cell carcinoma), high grade, aneuploid, TP53-mutated, hormone-receptor-negative tumors that are associated with a higher risk of metastasis and a poor prognosis (overall survival 55% at 5 years)

(Bokhman 1983). The prognostic value of this Bokhman's model was limited because high-grade lesions occur in 15–20% of endometrioid tumors. 20% of endometrioid, type I cancers recur but, on the other hand, half of type II cancers do not recur despite the higher risk. These type II, high-risk endometrial cancers account for approximately 10–15% of endometrial cancers, but cause 40% of deaths (Morice, Leary et al. 2016).

The most common endometrial cancer subtype is endometrioid adenocarcinoma (84%), which can be either histologically well differentiated (grade 1), moderately differentiated (grade 2) or poorly differentiated (grade 3). Other types are clearly less common: high grade serous cancer (HGSC) (4.5%), adenosquamous (4.2%), clear cell (2.5%), mucinous (0.9%), other (3.8%) (Di Saia, Creasman 2012).

Endometrioid adenocarcinoma grade 1–2 often develops through a premalignant change, atypical endometrial hyperplasia. The etiological factor is hyperestrogenism. Instead, atrophic endometrium develops an aggressive carcinoma, serous adenocarcinoma, which has a poor prognosis and resembles ovarian serous carcinoma (Di Saia, Creasman 2012).

Analysis of the cancer genome has discovered several mutations, and thus genetic factors form new subgroups of endometrial carcinoma. PIK3CA (90%), 26KRAS (20%) and FGFR2 (12%) mutations are often found in type I tumors. The Cancer Genome Atlas classifies four types of endometrial cancer based on mutations: specific p53, POLE and PTEN mutations, microsatellite instability and histology (the effect of metabolic factors on the development of cancer) (Morice, Leary et al. 2016, Suarez, Felix et al. 2017).

1.1.3 Prognostic factors

There are several prognostic factors for endometrial carcinoma (Table 2). The depth of myometrial invasion is one of the most significant factors. In deep invasion, the risk of lymph node metastasis is significantly higher than in superficial invasion (Larson, Connor et al. 1996 Di Saia, Creasman 2012).

Table 2. Prognostic factors for endometrial carcinoma

Prognostic factor	Poorer prognosis
The depth of myometrial invasion	In deep invasion, more than halfway through the uterus wall.
The tumor grade	Poorly differentiated (Grade 3) endometrioid carcinomas
The histologic type	Serous, clear-cell, undifferentiated carcinomas
The tumor site in the uterus	A tumor that is located low in the uterine cavity
The size of the tumor	A large size, >2cm
The lymphovascular invasion	Present
Peritoneal cytology	Positive
The lymph node involvement	Presence
Stage of disease	More advanced

1.1.4 Preoperative assessment

The main objective of preoperative assessment is to identify high-risk patients. Cancer histology defines the risk profile and is almost always used in the preoperative assessment. A sample is obtained by endometrial aspiration (e.g. Pipelle®), curettage or by a hysteroscopic biopsy. The grade and/or histologic type can change in the hysterectomy specimen, however (Neubauer, Havrilesky et al. 2009).

Deep invasion into the myometrium and tumor invasion into the uterine cervix is evaluated with imaging studies, such as ultrasound (US) and magnetic resonance imaging (MRI). US examination is easily available. Development of US technology has led to the implementation of 3D US that improves the assessment of invasion (Saarelainen, Vuento et al. 2012, Jantarasaengaram, Praditphol et al. 2014). In a Danish multicenter prospective comparative study that explored the sensitivity of MRI, positron emission tomography (PET/CT) and US examinations in the preoperative assessment of invasion depth in patients with endometrial carcinoma, the sensitivity was 87%, 93% and 71%, respectively (Beddy, O'Neill et al. 2012, Antonsen, Jensen et al. 2013).

In the early stage endometrial carcinoma, metastasis to the ovaries is rare, with an incidence of 4–5% (Gemer, Bergman et al. 2004, Boronow, Morrow et al. 1984). Thus, in young women with endometrial carcinoma, the ovaries may be spared when the stage is low, when no abnormalities are found in preoperative examinations and the operation includes a careful examination of the abdominal cavity (Lee, Lee et al. 2007).

1.1.5 Lymphadenectomy

Lymph nodes are not routinely removed from all cancer patients because the procedure also has adverse effects. It is primarily a diagnostic procedure to help the planning of sufficient adjuvant therapy. Lymph node surgical strategy is contingent on histological factors (subtype, tumor grade, involvement of lymphovascular space), disease stage (including myometrial invasion), patients' characteristics (age and comorbidities), and national and international guidelines (Morice, Leary et al. 2016). When the risk of lymph node metastasis is assessed as high, a pelvic and para-aortic lymphadenectomy is performed on the patient. and Lymph node metastasis are found in approximately 10% of the patients when a staging operation is performed, compared to only 1–3% when only suspicious lymph nodes are removed (Di Saia, Creasman 2012).

Several retrospective studies indicate that lymphadenectomy might also have therapeutic value (Cragun, Havrilesky et al. 2005, Larson, Broste et al. 1998, Katz, Andrews et al. 2001, Bristow, Zahurak et al. 2003, Onda, Yoshikawa et al. 1997). For example, Bristow et al. evaluated the potential survival benefit of removing all bulky nodes in Stage IIIC disease. They found that a complete removal provided a survival benefit of almost 30 months (p=0.006). (Bristow, Zahurak et al. 2003). The effect of lymphadenectomy on the prognosis has been studied in two randomized studies (Panici, Basile et al. 2008, Kitchener, Swart et al. 2009). but they did not show any effect of pelvic lymphadenectomy on the prognosis in local endometrial carcinoma. The practice of performing a pelvic lymphadenectomy on patients with low-risk endometrial carcinoma has largely been abandoned after the results of the extensive randomized study by Panici et al. became available. The study found that a systematic pelvic LND did not have any significant effect on the disease-free and overall survival time of the patients (Panici, Basile et al. 2008). Likewise, a recent retrospective cohort study implied that lymphadenectomy has only a modest, if any effect on the survival (Wright, Huang et al. 2016).

However, in two large studies lymphadenectomies has been found to be an independent prognostic factor in high-risk cancers. The National Cancer Institute of the United States organized a large SEER follow-up study in 1988–2001. The study followed 12,333 patients with intermediate-risk or high-risk (Stage IB, grade 3; Stage IC and II-IV, all grades) endometrial carcinoma. According to the results, the more extensive the lymphadenectomy, the more the 5-year survival prognosis improved. An extensive (in numbers) lymphadenectomy also improved the survival prognosis of stage IIIC-IV patients with lymph node metastasis (Chan, Cheung et al. 2006).

The randomized study of Todo et al. followed also patients with medium-high or high risk of recurrence and found that pelvic and para-aortic lymphadenectomy decreased the risk of death compared to patients who had only pelvic lymphadenectomy (Todo, Kato et al. 2010).

In serous carcinoma, a lymphadenectomy is performed unconditionally. The large material of Mahdi et al. from 1988–2007 included 4,718 women with serous endometrial carcinoma. Out of them, 68% underwent lymphadenectomy and 32% did not. Lymph node metastasis was found in 32% of the patients undergoing lymphadenectomy. In this material, lymphadenectomy was found to improve the prognosis in such a way that overall survival improved also in early-stage cancers. The more lymph nodes were removed, the more mortality decreased (Mahdi, Kumar et al. 2013).

1.1.6 Diagnosis and treatment

FIGO classification is used as the staging classification of endometrial cancer (Figure 1 and Table 3) (Colombo, Creutzberg et al. 2016, Mutch 2009).

As a basic principle, surgery includes removal of the uterus, the ovaries and the fallopian tubes. A cytological specimen is collected from the abdominal cavity. If cancer cells are detected in the abdominal cavity fluid, it does not change the FIGO staging classification but the result is given separately as an appendix to the stage class. The omentum is also removed in the case of serous histology.

Early stage endometrial cancers are potentially curative with surgical therapy. Adjuvant therapy is not recommended after surgery if the risk of tumor recurrence is small. Local radiotherapy of the vagina, brachytherapy, decreases the risk of cancer recurrence in the vaginal fornix. Cancer that has spread outside of the uterus is treated with pelvic radiotherapy and possibly para-aortic radiotherapy and chemotherapy or a combination of these (Colombo, Creutzberg et al. 2016).

In a metastatic disease (stage III–IV), the aim is optimal cytoreduction, and it is considered case-specifically whether a palliative operation is performed or neoadjuvant therapy with cytostatic agents or radiotherapy is given. Hormonal therapy can be considered for inoperable and debilitated patients, usually medroxyprogesterone acetate 250 mg/day. Hormone therapy is also indicated in advanced or recurrent endometrial cancer (Thigpen, Brady et al. 1999, Decruze, Green 2007).

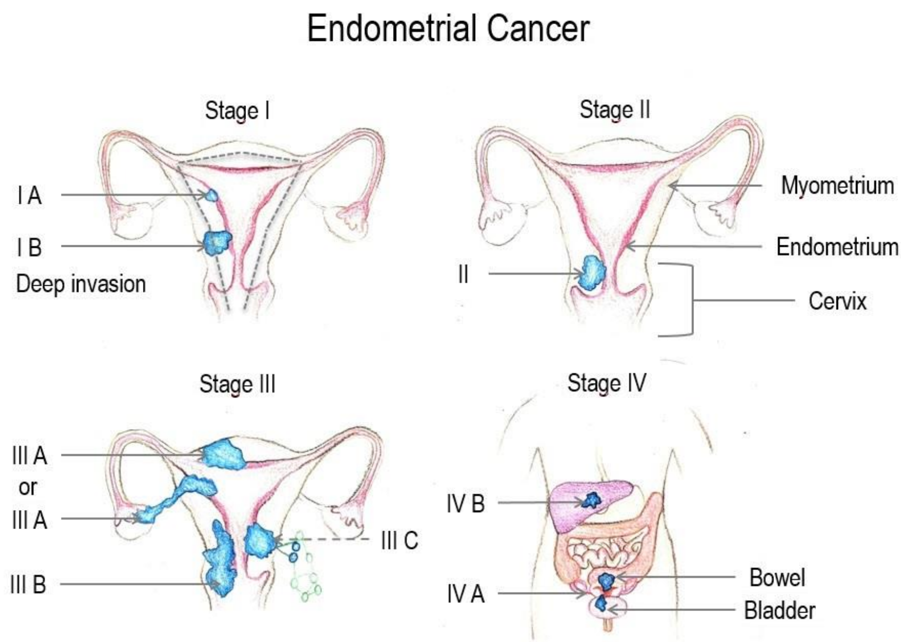


Figure 1. The staging classification of endometrial cancer

Table 3. Staging of endometrial carcinoma

Stage		Description
Stage I		Tumor confined to the corpus uteri
	IA	No or less than half myometrial invasion
	IB	Invasion equal to or more than half of the myometrium
Stage II		Tumor invades cervical stroma, but does not extend beyond the uterus
Stage III		Local and/or regional spread of the tumor
	IIIA	Tumor invades the serosa of the corpus uteri and/or adnex
	IIIB	Vaginal and/or parametrial involvement
	IIIC	Metastases to pelvic and/or para-aortic lymph nodes
	IIIC1	Positive pelvic nodes
	IIIC2	Positive paraortic lymph nodes with or without positive pelvic lymph nodes
Stage IV		Tumor invades bladder and/or bowel mucosa, and/or distant metastases
	IVA	Tumor invasion of bladder and/or bowel mucosa
	IVB	Distant metastases, including intra-abdominal metastases and/or inguinal lymph nodes
!		Positive cytology has to be reported separately

Postoperative risk class can be defined after the operation to guide adjuvant therapy (Table 4) (Colombo, Creutzberg et al. 2016). Postoperative risk classification requires a lymphadenectomy, except for stage IA patients, and assessment of adjuvant therapy sometimes calls for a new operation and a lymphadenectomy to assess possible metastasis, e.g. if the tumor is deeply invaded into the myometrium and lymph channel invasion is established or if histology changes to non-endometrioid.

Patients with low risk (Table 4) do not need adjuvant therapy. Intermediate and high-intermediate patients are given brachytherapy, especially when they are over 60 years old. High-risk patients are treated with either brachytherapy, cytostatic agents or cytostatic agents combined with radiotherapy, brachytherapy or whole pelvic radiotherapy (WPRT). Chemotherapy is commonly a combination of paclitaxel and carboplatin (Colombo, Creutzberg et al. 2016).

Table 4. Postoperative risk classification

Risk group	Description	Histology
Low	Stage IA, LVI neg.	Endometrioid grade 1-2
Intermediate	Stage IB, LVI neg.	Endometrioid grade 1-2
High-intermediate	Stage I, LVI +	Endometrioid grade 1-2
	Stage IA	Endometrioid grade 3
High	Stage IB	Endometrioid grade 3
	Stage II	All
	Stage III	Endometrioid
	Stage I-III	Non-endometrioid
Advanced	Stage III residual disease	All
	Stage IVA	All
Metastatic	Stage IVB	All

1.2 Cervical cancer

Cervical cancer is a global problem. Over half a million women develop this disease annually, 85% of whom live in less developed or developing countries. The cancer is most prevalent in Southern and Central Africa, and it is the most common type of cancer in women in these areas.

In the United States, 12,990 new cases of cervical cancer were diagnosed in 2016. Less than half (46%) of cervical cancer cases were found in the localized stage, 36% in the regional stage and 13% in the distant stage (in the Unites States, 2005–2011). In Finland, 175 new cases of cervical cancer were diagnosed in 2014. The incidence of cervical carcinoma in Finland has gradually increased over the last 20 years, being now 4.7/100,000 women. However, when organized Papanicolaou testing was introduced 50 years ago, age-standardized incidence was 14.6/100,000, and the annual number of new cancer cases was more than twice as high as now, 409 a year (www.cancerregistry.fi).

To detect preinvasive or early-stage invasive cancer, the Papanicolaou (Pap) test has been traditionally used sporadically and in organized screening programs (Salo, Nieminen et al. 2014, Nayar, Wilbur 2015). Recently, hr-HPV testing has been found to be more sensitive than Pap smear (Mayrand, Duarte-Franco et al. 2007) and initial experience on its use in the setting of organized screening has been published (Veijalainen, Kares et al. 2016).

Typically, the first symptom is postcoital bleeding followed by metrorrhagia or menorrhagia. At a later stage, the symptoms include anemia and rectal or bladder symptoms.

1.2.1 Risk factors

High-risk human papilloma viruses are considered to be the necessary causal factor in the cervical carcinogenesis, and hr-HPV has been found in 99.7% of cervical cancers (Walboomers, Jacobs et al. 1999). Out of these, especially HPV types 16 and 18, but also types 31, 33, 35, 39, 45, 52 and 58 are strongly associated with cervical cancer. 70% of cervical cancers cases are associated with either HPV16 (55%) or 18 (15%) infection. HPV18 is more common in cervical adenocarcinoma than in squamous cell carcinoma, where types HPV 16, 31, 33, 52 and 58 are prevalent (Walboomers, Jacobs et al. 1999, Smith, Lindsay et al. 2007).

Factors promoting the carcinogenic potential of persistent hr-HPV infection include: increased number of sexual partners, early age of first coitus, smoking, and chlamydia infection. Smoking is a risk factor that, combined with high-risk virus, multiplies the risk of developing malignant changes. (Di Saia, Creasman 2012, Luostarinen, Lehtinen 2004).

Preventive vaccines have been developed for hr-HPV (Apter, Wheeler et al. 2015, Mao, Koutsky et al. 2006, Villa, Costa et al. 2005, Koutsky, Ault et al. 2002, Harper, Franco et al. 2004, Kirby 2015). Therapeutic vaccines have also been studied extensively but none are on the market yet (Meyer, Fuglsang et al. 2014). In Finland, the bivalent HPV vaccine was included in the immunization program in 2013. (www.http://stm.fi/en/hpv-vaccinations).

1.2.2 Prognosis and stage

The main factors that influence the prognosis are tumor size, parametrial invasion of the tumor and lymph node spread at the time of diagnosis. The 5-year survival prognosis is good at (localized) early-stage (92%) but only 17% in metastatic disease. When considering all stages, the 5-year survival prognosis is 68% (Siegel, Miller et al. 2016). In Finland, the 1-year relative survival rate is 87% and 5-year relative survival rate is 65% (www.cancerregistry.fi).

Table 5. Carcinoma of the cervix uteri

Stage			Description
Stage I			The carcinoma is strictly confined to the cervix
	IA		Invasive carcinoma which can be diagnosed only by microscopy, with deepest invasion ≤ 5.0 mm and largest extension ≤ 7.0 mm
		IA1	Stromal invasion of ≤ 3.0 mm in depth and horizontal extension of ≤ 7.0 mm
		IA2	Stromal invasion of > 3.0 mm and not > 5.0 mm with an extension of not > 7.0 mm
	IB		Clinically visible lesions limited to the cervix uteri
		IB1	Clinically visible lesions ≤ 4.0 cm in greatest dimension
		IB2	Clinically visible lesions > 4.0 cm in greatest dimension
Stage II			Tumor extends outside cervix, but not to the pelvic wall or to the lower third of the vagina
	IIA		Without parametrial invasion
		IIA1	Clinically visible lesions ≤ 4.0 cm in greatest dimension
		IIA2	Clinically visible lesions > 4.0 cm in greatest dimension
	IIB		With obvious parametrial invasion
Stage III			Tumor extends to pelvic wall and/or involves lower third of vagina and/or causes hydronephrosis or non-functioning kidney
	IIIA		Tumor involves lower third of vagina, with no extension to the pelvic wall
	IIIB		Extension to pelvic wall and/or causes hydronephrosis or non-functioning kidney
Stage IV			The carcinoma has extended beyond the pelvis, or has involved mucosa of the bladder or rectum.
	IVA		Spread of the growth to adjacent organs
	IVB		Spread to distant organs

Cervical cancer is staged in theory clinically, according to the International Federation of Gynecologists and Obstetricians (FIGO) staging system, (Table 5) (Pecorelli 2009). However, imaging is practically always used in addition to clinical evaluation in developed countries. Magnetic resonance imaging (MRI) is the most reliable way of detecting if the cancer has spread to the parametrium outside the cervix. PET-CT (positron emission tomography) on the other hand is the most reliable way of detecting possible remote metastases (Selman, Mann et al. 2008). Because PET-CT is expensive and has limited availability, computed tomography (CT) is also widely used (Kumar, Dadparvar 2007).

1.2.3 Treatment

When the cancer is confined to the area of the cervix, it is treated operatively. The Finnish Gynecological Association recommends Stage IA1 and LVI negative cancers to be treated with conization or standard hysterectomy. For stage IA1 and LVI positive cancers, pelvic lymphadenectomy is performed because of risk for lymph node metastasis. (www.gynekologiyhdistys.fi/wp-content/uploads/2016/07/kelpohoitofingog62016.pdf.) Stage IA2–IIA cancer is treated with radical hysterectomy and pelvic and presacral lymphadenectomy (Oaknin, Rubio et al. 2015). The difference between radical hysterectomy and standard hysterectomy is the extent of the operation with regard to vagina and parametrial tissue. In radical hysterectomy, the ureters and bladder are mobilized from the tissue next to the uterine cervix, and parametrial tissue and vaginal cuff are included in the surgical specimen. is the goal with this technique is to achieve a healthy tissue margin around the removed cancer to improve the prognosis (Di Saia, Creasman 2012). In postmenopausal women, ovaries are often removed. They may be removed also in premenopausal women, according to the physicians' judgment. Cervical cancer is most commonly squamous cell carcinoma (76%) (Vizcaino, Moreno et al. 2000). In that case, it does not usually spread to the ovaries and it is not necessary to remove the ovaries. About in 20% of cases, cervical cancer is adenocarcinoma and is to some extent hormone dependent Adenocarcinoma spreads more easily to the ovaries, and the removal of ovaries is considered also in premenopausal women. Adenocarcinoma has a poorer prognosis, and the risk of death is 1.9-fold higher compared to squamous cell carcinoma (Gien, Beauchemin et al. 2010).

The main route of spread is through lymphatic pathways. Lymphadenectomy is standard treatment in stage IA1, LVI+ -IIA in several countries, including Finland. In addition to lymphadenectomy, the SLN (sentinel lymph node) method is being introduced to the surgery of cervical cancer. A systematic review of 67 studies on the SLN revealed that the pooled detection rate and sensitivity of SLN mapping in uterine cervical cancers are high: 89.2% and 90%, respectively (Kadkhodayan, Hasanzadeh et al. 2014). Lymphadenectomy is not performed in early-stage cancer, stage IA1, LVI–, because the risk of node metastasis is less than 1%. The only necessary treatments are standard hysterectomy or conization. Hematogenous spread is rare.

In nulliparous women, when the stage is IA2–IB1, gr 1–2, LVI–, tumor size <2 cm and there is no lymph node metastasis, a fertility-sparing radical trachelectomy can be performed where the uterine cervix and adjacent tissues are removed but the uterine corpus is spared (Shepherd 2012, Oaknin, Rubio et al. 2015).

Extended or radical hysterectomy is a demanding procedure to be performed using traditional laparoscopy, especially taking into account the present demand for a nerve-sparing technique. Thus, radical hysterectomy is perfectly suited to robotic-assisted surgery (Lambaudie, Narducci et al. 2010, Gorchev, Tomov et al. 2013).

Surgery is usually a sufficient treatment in stage I–IIA cervical cancer, when the specimen has clean margins and there are no metastatic lymph nodes. Patients with stage IIB–IV cervical cancer are not in general candidates for operative treatment. Stage IIB-IVA cancers can still be curatively treated with (chemo)radiation and brachytherapy, and sometimes Stage IVA cancer can be salvaged with pelvic exenteration. (Shepherd 2012, Oaknin, Rubio et al. 2015)

In persistent, recurrent or metastatic cancer, combining bevacizumab to paclitaxel and cisplatin/topotecan chemotherapy improves the prognosis (Tewari, Sill et al. 2014).

1.3 Ovarian cancer

The global incidence of ovarian cancer is 220,000 new cases/year (Jayson, Kohn et al. 2014). In the United States in 2016, ovarian cancer was not among the ten most common cancers diagnosed in women but cancer of the corpus uteri was the fourth most common. There in the same year, 22,280 new cases of ovarian cancer were diagnosed, and ovarian cancer was the fifth most common cause (5%) of cancer deaths (14,240) (Siegel, Miller et al. 2016).

The five-year relative survival rate for ovarian cancer (United States, 2005–2011) is poorer than for endometrial or cervical cancer. When all stages are considered, it is 46%. If the cancer is diagnosed in the localized stage, the five-year survival prognosis is 92%, but only 15% of all cases are diagnosed in this stage. 19% of the cases are diagnosed in the regional stage, in which case the 5-year survival prognosis is 73%. Over half (60%) of ovarian cancer cases are diagnosed in the metastatic phase, in which case the 5-year survival prognosis decreases to 28% (Siegel, Miller et al. 2016).

In Finland, 530 new ovarian and fallopian tube cancers are diagnosed annually (diagnoses in 2010–2014), and their incidence is 9.5/100,000. The 1-year relative survival rate is 78% and the 5-year relative survival rate is 45%, on the same level as in the United States (www. cancerregistry.fi).

1.3.1 Risk factors

Incessant ovulations not interrupted by pregnancies are considered as a risk factor for ovarian cancer. Thus, anovulation induced by pregnancy and/or the use of oral contraceptives decreases the morbidity risk (Tsilidis, Allen et al. 2011). The risk may also be decreased by tubal ligation (Sieh, Salvador et al. 2013). However, endometriosis (Munksgaard, Blaakaer 2012, Wiegand, Shah et al. 2010) and polycystic ovaries (Chittenden, Fullerton et al. 2009), as well as childlessness and later age at menopause are associated with ovarian cancer (Jayson, Kohn et al. 2014, Di Saia, Creasman 2012). Epithelial ovarian cancer is a major element in several germline genetic mutation syndromes, the most common are associated with defective homologous recombination DNA repair, such as the BRCA1 and BRCA2 genes (Di Saia, Creasman 2012, Antoniou, Pharoah et al. 2003).

1.3.2 Diagnosis

Ovarian cancer is more common in postmenopausal women, and the first symptoms typically include abdominal pain and abdominal distention that last for 3–4 months. The median age at time of diagnosis is 63 years (Jayson, Kohn et al. 2014).

Preoperatively, the nature of ovarian tumors is generally characterized by ultrasound and CT imaging and blood tests, based on Ca 12-5 and HE4 values, etc. In ovarian cancer diagnoses, the specificity of Ca12-5 value is 97% and sensitivity 57-75% (Di Saia, Creasman 2012). Clinical experience of the ultrasound examiner improves the sonographic assessment (Niemi, Saarelainen et al. 2017).

Ovarian cancer is not one disease. The largest group of ovarian cancer is high-grade serous carcinoma (70%), and tubal fimbriae might be the site of origin of most high-grade serous cancers (Kindelberger, Lee et al. 2007, Medeiros, Muto et al. 2006). Other epithelial ovarian cancer subtypes are low-grade serous (less than 5%), endometrioid (10%), clear cell (10%) and mucinous (3%) (Jayson, Kohn et al. 2014, Mutch, Prat 2014).

Dissemination of ovarian cancer involves hematogenous or lymphatic dissemination and exfoliation. Because of lymphatic dissemination, lymphadenectomy is performed in both the pelvic and para-aortic region. Lymph node metastasis has an effect on the FIGO staging classification (Table 6) (Mutch, Prat 2014).

Prognostic factors for OS and PFS are patient's age, medical co-morbidities, FIGO stage, postoperative residual disease, tumor biology, presence of large volume ascites (≥ 500 mL) and poor response to chemotherapy (Bois, Reuss et al. 2009).

Table 6. FIGO staging of ovarian cancer

Stage		Description
Stage I		Tumor confined to the ovaries or fallopian tube(s)
	IA	Tumor in one ovary (capsule intact) or tube, cytology neg.
	IB	Tumor in both ovaries (capsule intact) or tubes, cytology neg.
	IC	Tumor in one/both ovaries/tubes, tumor rupture or cytology +
Stage II		Tumor(s) with pelvic extension
	IIA	Extension in gynecological organs
	IIB	Extension in other pelvic tissues
Stage III		Metastasis in lymph nodes
	IIIA	Metastasis in lymph nodes
		A1: Positive retroperitoneal lymph nodes only, metastasis (i) ≤10mm (ii) >10mm
		A2: Microscopic extrapelvic involvement
	IIIB	Macroscopic peritoneal metastasis beyond the pelvis, ≤ 2cm
	IIIC	Macroscopic peritoneal metastasis beyond the pelvis, > 2cm
Stage IV		Distant metastases excluding peritoneal metastases
	IVA	Pleural effusion
	IVB	Metastasis to extra-abdominal organs, parenchymal metastases

1.3.3 Treatment

Preoperative assessment of ovarian tumor diagnosis has generally to be confirmed at an operation. When cancer is suspected, a frozen section is collected from the ovarian tumor and extended surgery is anticipated. The extent of surgery is decided based on the frozen section result and patient history.

Ovarian cancer is treated by surgery where the aim is maximal cytoreduction, i.e. complete or maximal removal of the tumor. In the best case, the tumor is removed completely. This is called optimal surgical outcome (R0). In addition to the ovarian tumor, the ovaries, the fallopian tubes, the uterus, the omentum, the appendix as well as pelvic and para-aortic lymph nodes are removed, and a cytological specimen is collected from the abdominal cavity (Bristow, Tomacruz et al. 2002, Aletti, Dowdy et al. 2006, William E. Winter III, Maxwell et al. 2007, Eisenkop, Friedman et al. 1998, Chi, Franklin et al. 2004, Bois, Reuss et al. 2009).

As a rule, lymphadenectomy is performed in the case of epithelial ovarian cancer. An exception to this is, however, mucinous early-stage (stage I) ovarian cancer. In early stage disease, lymphadenectomy per se does not improve the prognosis, but it allows a more accurate staging. (Maggioni, Panici et al. 2006). Lymphadenectomies are also recommended in stage III–IV, if the surgical outcome is nearly optimal or if lymphadenectomy helps to reduce the amount of residual tumor. According to the most recent research, lymphadenectomy does not impact life expectancy in metastatic ovarian cancer, and if the lymph nodes are normal on palpation, it may not be necessary to remove them in the operation (Fotopoulou, El-Balat et al. 2015, Harter, Sehouli 2017). Lymphadenectomy is necessary for defining FIGO staging but it does not have any survival benefits (Panici, Maggioni et al. 2005). Lymphadenectomies are performed on women desiring for future pregnancy, who are candidates for surgery that spares the uterus and one ovary, when the stage is IA.

A frozen section is not always possible and the result of frozen section can also change in the final histopathological report. In such cases, staging operation may be necessary., Laparoscopic restaging surgery is very feasible, and lymphadenectomy can be performed during the operation as safely as in laparotomy (Leblanc, Querleu et al. 2004, Nezhat, DeNoble et al. 2010, Spirtos, Eisekop et al. 2005, Chi, Abu-Rustum et al. 2005).

Para-aortic lymphadenectomy is usually performed as an open surgery for ovarian cancer, but surgery for early stage cancer or staging re-operation can be performed laparoscopically, in which case the robotic-assisted para-aortic lymphadenectomy is a valid alternative (Magrina, Magtibay 2011, Brown, Mendivil et al. 2014).

In metastatic disease, the aim is to remove the cancer radically, e.g. from surfaces of the peritoneum, the dome of the diaphragm and the abdominal cavity. The operation can include, for example, bowel resection, diaphragm resection, splenectomy and liver resection. Optimal cytoreduction increases the prognosis two or three-fold (Harter, Muallem et al. 2011). Several studies have found that complete cytoreduction is the most important factor for improving survival. (Aletti, Dowdy et al. 2006, Chi, Eisenhauer et al. 2006, William E. Winter III, Maxwell et al. 2007, Bois, Reuss et al. 2009). Three randomized studies conducted in 1995–2002 included 3,388 patients with ovarian cancer. They found that median life expectancy was clearly longer (99 months) in patients with no residual tumor, compared to patients with residual tumor of 1–10mm (36 months) and >10mm (30 months), $p<0.0001$. (Bois, Reuss et al. 2009).

In order to achieve optimal surgical outcome, the operations have lately been assigned to gynecologic oncologists (Eisenkop, Eisenkop et al. 1992, Earle, Schrag et al. 2006). For example, in a study conducted in Germany in 2004–2008, optimal result was reached by oncologists in 62% of operated patients (n=396), when the corresponding rate for non-oncologists was 33% in 1997–2000. The median OS increased from 26 months to 45 months in patients operated on by gynecologic oncologists ($p< 0.003$) (Harter, Muallem et al. 2011).

Factors that may prevent complete primary debulking surgery include extensive upper abdominal disease, involvement of the porta hepatis, small bowel mesentery and diaphragm or spread beyond the abdominal cavity (Aletti, Gostout et al. 2006). In metastatic ovarian cancer (stage IV), patients who also have poor performance or nutritional status (low preoperative albumin) and are over 75 years old are not candidates for radical surgery because of clearly increased morbidity (64%) and limited surgical benefits. This group includes approximately 7% of the patients (Aletti, Aletti et al. 2011).

However, it is difficult to assess preoperatively whether complete debulking is possible in the operation or not (Bristow, Duska et al. 2000, Dowdy, Mullany et al. 2004, Memarzadeh, Lee et al. 2003, Berchuck, Iversen et al. 2004, Axtell, Lee et al. 2007, Chi, Venkatraman et al. 2000). Neo-adjuvant chemotherapy (NACT) is widely used when ovarian cancer has spread to the abdominal cavity and it is assessed that the optimal result cannot be reached with the primary operation. In such cases, chemotherapy is given to reduce tumor growth. After 3–4 chemotherapy cycles, an interval debulking surgery (IDS) is performed with the aim of achieving optimal surgical outcome. If optimal surgical outcome is not possible based on the assessment, chemotherapy is usually continued (Wright, Bohlke et al. 2016).

According to a meta-analysis of 21 non-randomized trials the survival was similar in patients treated with neoadjuvant chemotherapy followed by interval debulking surgery compared to primarily debulked patients (Kang, Nam 2009). Vergote et al. in a randomized study in patients with stage IIIc and IV ovarian cancer found that the survival was similar for in these two ways (Vergote, Trope et al. 2010). A randomized study (CHORUS) compared primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer. In stage III or IV, no significant difference in survival time (24.1 months vs. 22.6 months) was detected between the groups, and both techniques were found to be acceptable (Kehoe, Hook et al. 2015).

As a rule, platinum-based combination chemotherapy is recommended after the surgery (Trimbos, Vergote et al. 2003, Trimbos, Parmar et al. 2003, Trimbos, Timmers et al. 2010). Six cycles of a combination of paclitaxel and carboplatin are a common practice, but more cycles can be considered based on the response. Carboplatin is used as a single agent when the patient's performance or underlying disease contraindicate the use of paclitaxel. Adding bevacizumab (anti-vascular endothelial growth factor monoclonal antibody) to the treatment can be considered when the stage is IIIB, IIIC and the surgical outcome is suboptimal (size of the residual tumor > 1 cm) or IV. The length of bevacizumab treatment is 15 months (Perren, Swart et al. 2011, Burger, Brady et al. 2011).

1.4 Surgical techniques in gynecologic oncology

Different surgical techniques have been developed over time, and general technical advancement is also evident in medicine. Increase in anatomical knowledge has had a major role in surgical development. The oldest, most traditional and still the best technique in the view of many is open surgery, i.e. laparotomy. It has been complemented with the new mini-invasive surgical techniques laparoscopy and lately robotic-assisted laparoscopy. The mini-invasive technique has distinct benefits: reduced estimated blood loss (EBL), shorter hospital stay and faster recovery which are especially significant for elderly and possibly debilitated cancer patients. Mini-invasive techniques also include issues that call for consideration. It has been contemplated if a similar oncological result is reached with a mini-invasive technique compared to open surgery, how learning curve affects the operations and how the costs should be viewed. Hospitals, instruments, surgeons and patients are all different. Several factors have an effect on the decision: the type of cancer, cancer stage, patient's age and weight, patient's health, instruments available in the hospital, the surgeon's skills and knowledge of the benefits and adverse effects of the different techniques (Conrad, Ramirez et al. 2015).

1.4.1 Laparotomy

The first successful open surgeries for gynecological indications were performed approximately 200 years ago. Most of them did not include anesthesia or use of aseptic technique, and mortality was high. The Briton Robert Tait (1845–1899) can be seen as an important pioneer in gynecologic surgery. He introduced aseptic technique and handling of tissue in the operations, which clearly reduced mortality. In 1872, Tait reported on the first series of ovariotomies on 9 patients, out of which only 1 woman died. 14 years later, in 1886, he reported on 139 consecutive ovariotomies without a death. Mortality reduced to 3–4%, when it had been 25–30% with earlier surgeons. In 1884, he traveled to Canada and the United States to give lectures and to perform operations. As a result, surgery in the abdominal cavity and pelvic region started developing in these countries as well (Golditch 2002).

In 1912, Wertheim, an Austrian surgeon, published a description of radical hysterectomy based on 500 cases of cervical cancer. In addition to radical hysterectomy Wertheim only removed the abnormal lymph nodes and did not support systematic lymphadenectomy. In the 1940s, surgeon Meigs published better survival rates when routine pelvic lymphadenectomy was included in the procedure. For that reason, radical hysterectomy is often called Wertheim-Meigs operation. Schauta is seen as the pioneer of radical vaginal hysterectomy. He developed technique of vaginal removal of the parametrium whereas Wertheim did it abdominally (Swailes, Gockley et al. 2017). In 1987, Daniel Dargent modernized the radical vaginal hysterectomy by combining it with laparoscopic lymphadenectomy (Swailes, Gockley et al. 2017). Afterwards, laparoscopic technique has been developed the most (Querleu 1993, Canis, Mage et al. 1990), and laparoscopy has been strongly favored in the 21st century (Sharma, Bailey et al. 2006).

1.4.2 Vaginal technique

The vaginal technique is used with laparoscopy in oncological operations, such as laparoscopy-assisted standard or radical hysterectomy or trachelectomy, laparoscopic part of the operation allows inspection of the abdominal cavity, collection of a cytological specimen and lymphadenectomy, when necessary. In 1993, a pilot study of eight cases of radical surgery for cervical carcinoma was published. It utilized the benefits of both surgical techniques: lymph nodes were removed, proximal head of the uterine artery was prepared and the ureter was mobilized in laparoscopy, and a sufficient amount of vaginal cuff was removed vaginally (Querleu 1993).

In endometrial cancer, if the patient e.g. has contraindications for general anesthesia, the uterus can be removed vaginally. This is most common in the case of morbid obesity, significant cardiopulmonary medical comorbidities and advanced age. prognosis of these patients operated vaginally in an early stage of cancer is comparatively good. The reported 3-year and 5-year survival rates in such cases are 91% and 88%, respectively (Di Saia, Creasman 2012).

1.4.3 Laparoscopic technique

In European literature, minimally invasive gynecologic procedures are first mentioned in 1928. During the next 30 years, minimally invasive diagnostic procedures evolved, including hysteroscopy, pelviscopy and laparoscopy. In the 1960s, there were significant improvements to laparoscopy, such as a pressure-controlled carbon dioxide insufflator, an extra-abdominal light source and a uterine manipulator. The procedures were mainly diagnostic. More series of procedures were described in the 1960s and 1970s, but the procedures were quite modest: tubal ligation and small biopsies. As technology improved and experience increased in the 1980s, operative laparoscopy was introduced, including ectopic pregnancy, subserosal myomas and endometriosis. By the late 1980s, case reports were emerging of minimally invasive techniques used by gynecologic oncologists (Abaid, Boggess 2005).

Laparoscopic hysterectomy was first described by Reich et al. in 1989 (Reich, DeCaprio et al. 1989). The first laparoscopic hysterectomy in Finland was performed in September 1992 (Mäkinen, Sjöberg 1994), and by 1996 already 24% of hysterectomies performed for benign causes were laparoscopic (Mäkinen, Johansson 2001). Twenty years ago, results were published from studies on learning curves of laparoscopic operations in gynecologic surgery. According to them, the learning curve for traditional laparoscopy is long, or over 125 procedures (Melendez, Childers et al. 1997) Similarly, in a Finnish study the operating time was shortened during the first one hundred laparoscopic hysterectomies (Härkki-Siren, Sjöberg et al. 1995). Surgeons who had performed over 30 laparoscopic hysterectomies had a significantly lower rate of complications (Mäkinen, Johansson 2001).

In laparoscopic surgery, the first incision (approximately 2cm) is made below the umbilicus, and for access to the abdominal cavity either an open technique or the insertion of a Veress needle through the umbilicus is used. A pneumoperitoneum has to be created to gain working space before a camera is inserted through the umbilical trocar shell into the abdominal cavity. A few, generally 4–6, small incisions for auxiliary trocars are then made. Instruments needed for the intra-abdominal procedures are inserted through the trocar shells. There are different instruments for different purposes, e.g. scissors and forceps. Electric current, monopolar or bipolar, can be conducted to the instruments to achieve hemostasis. The light wire attached to the camera are controlled by the laparoscopy tower or camera. In gynecology, the removal of the uterus naturally opens a pathway into the vagina that can be used for removing tissues of the abdominal cavity (Di Saia, Creasman 2012.)

Laparoscopic lymphadenectomy became rapidly popular at the end of the 1990s and the beginning of the 21st century. Abu-Rustum et al. performed laparoscopic transperitoneal pelvic and/or para-aortic lymphadenectomy in 203 patients with gynecologic malignancies. The procedure was successfully performed using laparoscopy in 114 patients (56%). The mean number of pelvic and para-aortic nodes was 10.7 and 5.7, respectively, mean EBL was 151 ml and mean hospital stay was 2.8 days and post-operative complications 7% (Abu-Rustum, Chi et al. 2003). The study of Magrina et al., carried out at the end of the 1990s, found that in the treatment of endometrial carcinoma, laparoscopy leads to similar 3-year survival than the previous surgical techniques. (Magrina, Mutone et al. 1999) After laparoscopy, the rate of port-site metastasis has been found to be 1.4% (Childers, Childers et al. 1994).

Mabrouk et al. conducted a survey on the use of laparoscopy by Society of Gynecologic Oncology (SGO) members in the United States in 2007. 388 members out of 850 members answered the survey (46%). 352 of the respondents (91%) reported that they used laparoscopic surgery compared with 84% in the 2004 survey. The three most common procedures were: hysterectomy and staging operation for uterine cancer (43%), diagnostic laparoscopy for adnexal masses (39%), and prophylactic bilateral oophorectomy for high-risk women (11%) (Mabrouk, Frumovitz et al. 2009).

1.4.3.1 Laparoscopy compared to laparotomy

In the beginning of the 21st century, several randomized studies were conducted that compared laparotomy and laparoscopy in the treatment of endometrial carcinoma (Janda 2010, Tozzi, Malur et al. 2005, Zullo, Palomba et al. 2005, Mourits 2010). In all operations, operation time was longer in the laparoscopy group but quality of life was invariably better after laparoscopy. In the comparative studies, the total complication rate for laparotomy was as high as 39%, compared to 6–30% when using laparoscopy (Malur, Possover et al. 2001, Gemignani, Curtin et al. 1999). No significant differences were found in overall and disease-free survival after the long-term follow-up period of 6.5 years in a randomized controlled trial (Zullo 2009).

It was only after enough evidence-based data became available that laparoscopy established its status as a safe and recommendable surgical technique. Transition to mini-invasive technique has been relatively slow. As late as 2008, 64% of hysterectomies were performed using laparotomy and only 14% using laparoscopy in the U.S. (Jacoby, Autry et al. 2009). In Finland of all hysterectomies for a benign condition, 24% were laparoscopic and 58% were abdominal in 1996, while the corresponding figures in 2006 were 32% and 24%, respectively. The proportion of VHs increased from 18% in 1996 to 44% in 2006 (Brummer, Jalkanen et al. 2009, Makinen, Brummer et al. 2013).

In 2009, the Gynecologic Oncology Group (GOG) published a large randomized comparison study (GOG-2222 or LAP2) on the differences of laparoscopy and laparotomy in the treatment of patients with endometrial carcinoma. The LAP2 study included 2,616 surgical patients, out of which laparoscopy was used in 1,696 patients and laparotomy in 920 patients. After this study, mini-invasive surgery gained more popularity. The study found that laparoscopy was a safe and feasible technique without increased risk of recurrence of cancer, to use in staging operations on patients with endometrial carcinoma, when compared to open technique. In laparoscopy group, the incidence rate of moderate/severe postoperative complications was 14%, compared to 21% in the laparotomy group. The rate of intraoperative complications was 10% vs. 8%, respectively. Surgical treatment also included a lymphadenectomy. Conversions were common, they were made in 25.8% of the cases (Walker, Piedmonte et al. 2009, Kornblith, Huang et al. 2009). At 3 years, recurrence rate was 11.4% in the laparoscopy group and 10.2% in the laparotomy group. The 5-yr overall survival was identical in both groups, 89.8% (Walker, Piedmonte et al. 2012).

In a Dutch study, 283 patients with Stage I endometrial carcinoma were randomized 2:1 to laparoscopy (n=187) and laparotomy (n=96). There was no significant difference in complications between these two groups. In the laparoscopy group, 14.6% of the patients had major complications, 13.0% minor complications. The corresponding rates in the laparotomy group were 14.9% and 11.7%, respectively. Conversions were performed in 10.8% of the patients in LH group. In the laparoscopy group, the amount of bleeding ($p<0.0001$), use of painkillers ($p<0.0001$), length of hospital stays ($p<0.0001$) and length of recovery ($p=0.002$) were significantly lower, but the operation time was longer ($p<0.0001$) (Mourits 2010).

. The quality of life (QoL) was perceived to be better after laparoscopy (LAP2), especially at 6 weeks after the surgery (Kornblith, Huang et al. 2009). The LACE study compared the quality of life (QoL) between patients that underwent LH and laparotomy for endometrial cancer. Among the LH patients, the quality of life was better both at 3 and at 6 months after the surgery. A faster recovery and smaller amount of complications were seen to contribute to the better quality of life (Janda 2010).

Hysterectomies due to endometrial carcinoma in 2006–2010 using laparotomy vs. mini-invasive surgery (MIS) were studied in the United States using the database of the American College of Surgeons–National Surgical Quality Improvement Project. The study included 2,076 women, out of which 1,269 were operated using laparotomy and 807 using MIS technique. The mini-invasive technique included laparoscopy, laparoscopy-assisted vaginal hysterectomy and robotic-assisted technique. The proportion of MIS technique was only 16% in 2006 and 48% in 2010. In the MIS group, operation time was longer than in open surgery but the number of complications was significantly lower in the MIS group (n=97, 12%) vs. the laparotomy group (n=398, 31.3%), ($p< 0.0001$), and the length of hospital stay was shorter. The complications included especially wound complications, pneumonia, re-intubation, renal insufficiency, bleeding with transfusions, and septic shock (Scalici, Laughlin et al. 2014).

The same trend has been seen in the surgery of cervical cancer and endometrial carcinoma. Traditional laparoscopy is challenging in the treatment of cervical carcinoma, and robotic-assisted laparoscopy has introduced advanced instruments/techniques that potentially improve the surgery of cervical carcinoma (Magrina, Zanagnolo 2008). In laparoscopic surgery for cervical cancer, urinary tract trauma is a clear risk in the early stages of the learning curve (Sharma, Bailey et al. 2006).

Open and endoscopic radical hysterectomy produce similar survival rates. The amount of bleeding and the length of hospital stay were higher in open operations (Mendivil, Rettenmaier et al. 2016). E.g. Halliday et al. reported that intraoperative bleeding was over five times higher in open operations compared to robotic-assisted surgery (546 vs. 106 ml) (Halliday, Lau et al. 2010a). Several studies have showed that MIS technique decreases the amount of intraoperative bleeding, the need for transfusions, the number of complications and the length of hospital stay when compared to open surgery, but it increases the duration of the operation (Frumovitz, dos Reis et al. 2007, Puntambekar, Palep et al. 2007, Holloway, Finkler et al. 2007, Zakashansky, Lerner 2008).

In ovarian cancer, the first reports of laparoscopic staging operations were published at the beginning of the 1990s (Querleu 1993, Querleu, LeBlanc 1994, Childers, Lang et al. 1995, Pomel, Provencher et al. 1995). Retrospective studies suggested that laparoscopic staging was a safe and feasible technique in early-stage ovarian cancer when compared to open surgery. Additionally, no difference in recurrence of cancer were found between the surgical techniques (Tozzi, Köhler et al. 2004, Jung, Lee et al. 2009, Nezhat 2009).

1.4.4 Robotic-assisted laparoscopic technique

The main difference between robotic-assisted and traditional laparoscopy is that the surgeon does not touch the patient's tissues himself or herself but uses a technical device, which translates the surgeon's actions into robotic movements. This technique requires three components: a robot, a console and the vision system (Figure 2). The robot, which has 4 movable arms, is attached to the trocars inserted in the patient's abdominal cavity. A camera is attached to one robotic arm and surgical instruments are attached to the other three arms. The surgeon uses the robotic arms and instruments attached to the patient with the handles and foot pedals in the console. The electric current (monopolar and bipolar) is also selected with foot pedals (Intuitive Surgical company website. Available from: https://www.intuitivesurgical.com/company/profile.php [Last accessed on 2017 August]) (Chen, Falcone 2009, Holloway, Patel et al. 2009, Nezhat 2008, Lin, Wakabayashi et al. 2009).

Robotic-assisted surgery has been widely implemented in gynecologic oncology without any randomized prospective studies. The same phenomenon was seen earlier with laparoscopy, which was also taken into use without convincing research evidence (Abaid, Boggess 2005). Four randomized studies have been published on benign gynecological surgery (Sarlos, Kots et al. 2012, Paraiso, Ridgeway et al. 2013, Paraiso, Jelovsek et al. 2011, Anger, Mueller et al. 2014) showing no benefit of robotic-assisted technique when compared to traditional laparoscopy.

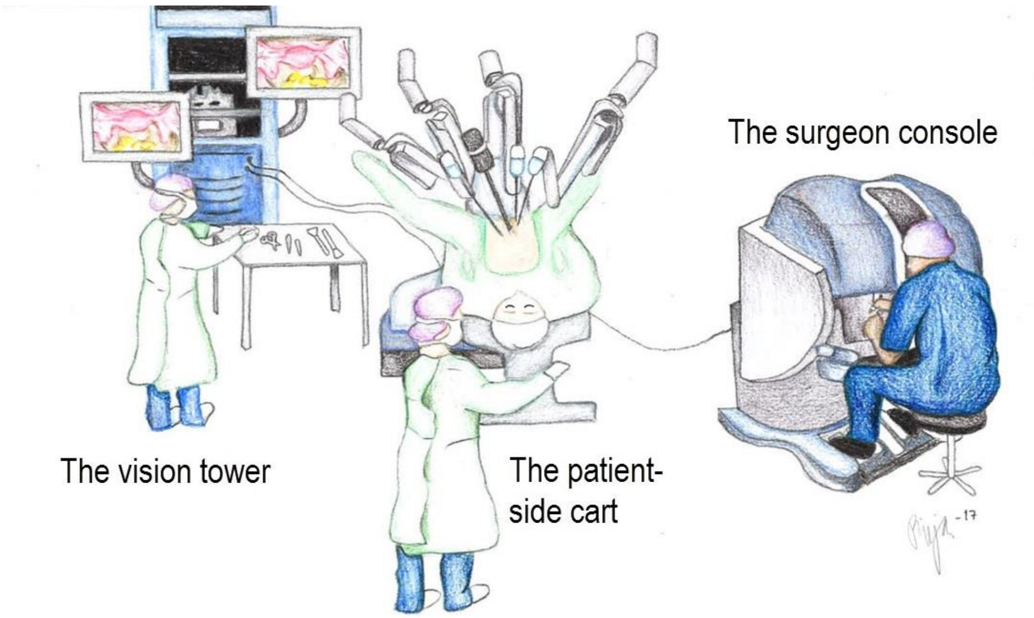


Figure 2. Robotic-assisted laparoscopy technique components:

the vision system, robot and console

1.5 Robotic-assisted surgery

1.5.1 Development of the robotic-assisted surgery

The need for telesurgery in the 1980s is seen as the starting point for robotic-assisted surgery. Back then it was developed from the perspective of space and military medicine. Puma 569 was the first robotic device and it was used for brain biopsy in 1985. In 1987, 30 years ago, the first robotic-assisted cholecystectomy was performed, and in 1988, prostate surgery was started in London using a device called the Probot. The next robotic device was the Robodoc, which was used for hip replacement surgery in 1992. During the 1990s, robotic technology advanced and the robotic arms of the Zeus Surgical System were navigated with speech commands, such as "move right" or "stop". Also, telesurgery was performed. The new robots developed in the 1990s also included robots called Aesop and Hermes. After these versions, the da Vinci robot that is still in use was developed. It was the leading technological accomplishment and was introduced to the market without any competitors (Mendivil, Holloway et al. 2009, Mettler, Schollmeyer et al. 2008).

The da Vinci S was the first model of Surgical System, and it was used in an operation for the first time 20 years ago in Belgium. In 1999, FDA approved the surgical robot da Vinci for surgical use, and in 2005 for gynecologic surgery. In 2005–2006, the number of robotic-assisted laparoscopy operations grew rapidly, and publications started appearing from 2005 (Mendivil, Holloway et al. 2009). The da Vinci Si and Xi were the next updates of the robot in 2009 and 2014, respectively (https://www.intuitivesurgical.com/training/). So far, there are no other robot brands available for robotic-assisted surgery.

In addition to urology and gynecology, robotic-assisted surgery is used in other fields of surgery, such as gastric, thoracic and cardiovascular surgery as well as pediatric and ENT surgery. At first, robotic-assisted surgery rapidly became more common in urology, but in recent years, the strongest global growth has been seen in gynecology.

1.5.2 Special characteristics of robotic-assisted surgery

Robotic-assisted surgery has certain special characteristics that other surgical techniques lack. (Table 7 and Figure 3).

Table 7. Characteristics of robotic-assisted surgery

The advantages of the robotic-assisted surgery
The 3D view: - better and more precise visibility of the operation area
- good perception of the tissues and distances
- makes coordination between the eyes and the hands easy
Excessive movement are filtered out
- hand tremor
- robot hands are tireless
The movement of the instruments' wrist is similar to the hand movements of the surgeon in open operations
The tips of surgical instruments are small
The better mobility and the greater range of movement of the instrument head all facilitate
The camera is stable and stays in the desired position
The surgeon has an ergonomic working position

The range of motion of the hand and wrist can be translated into navigating the instruments but on a smaller scale, a 6cm movement of the wrist corresponds to 2cm movement of the robotic instruments in the abdominal cavity. Characteristics of robotic-assisted surgery potentially in a more precise technique and is reduced tissue damage (Ben-Or, Nifong et al. 2013, Ramirez, Adams et al. 2012, Palep 2009, Holloway, Patel et al. 2009, Nezhat 2008). Robotic-assisted surgery highlights the good features of laparoscopy: small amount of intraoperative bleeding, smaller risk of complications and faster recovery resulting in shorter hospital stay and sick leave (Nezhat 2008, Cho, Nezhat 2009, Lim, Kang et al. 2011).

The downside of robotic-assisted surgery is the lack of tactile feedback and the loss of peripheral vision (Oehler 2009). It is also clumsy to move the arms and instruments in extensive surgical fields, especially when using the first two models of da Vinci robot. Equipment of the robotic system requires much space in the operating room. The surgical position of the patient is a deep Trendelenburg position, and the patient's condition must allow remaining in that position for the duration of the operation. This has to be considered when planning the operation because the position cannot be changed in the middle of the operation without de-docking the robot from the patient (Holloway, Patel et al. 2009). In the new Xi robotic model this problem has been corrected and the position can be changed during the operation (https://www.intuitivesurgical.com/training/).

Although the working position of the surgeon is more ergonomic than in traditional laparoscopy, the console working is associated with physical symptoms or discomfort, like pain, neck stiffness, numbness, and finger and eye fatigue (Lee, Lee et al. 2016, McDonald, Ramirez et al. 2014).

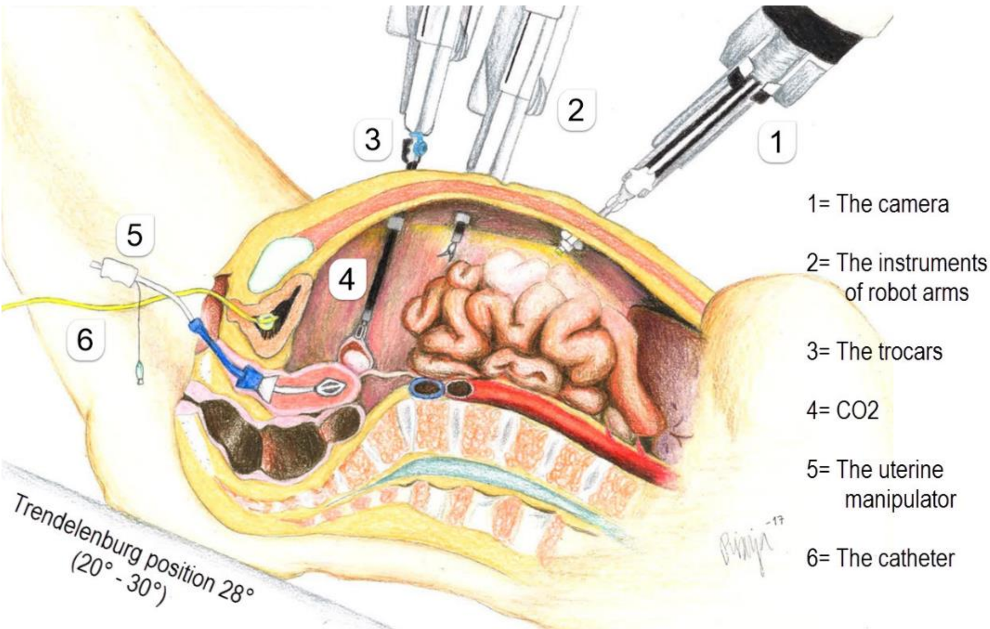


Figure 3. Characteristics in robotic-assisted laparoscopy operation

1.5.2.1 Trocars

Robotic-assisted surgery is started in the same way as traditional endoscopic surgery, by inserting a manipulator into the uterus when appropriate and trocars into the abdominal cavity. The first trocar, the camera port, is usually introduced using an open approach, but alternatively a Veress needle can be inserted first and gas conducted through it. The abdominal cavity is inflated with gas and a camera introduced into the abdominal cavity, and the rest of the trocars are inserted under visual control. Three 8 mm trocars are placed to allow attachment of the robotic arms, and 1 to 2 additional trocars are placed for assistant use. The usual number of trocars is 5 to 6, but it varies a lot depending on their insertion site in the abdominal wall. Their location is based on the procedure, the surgeon and the size of the patient. The distance between the robotic trocars should be at least 8 cm, to allow sufficient movement of the robotic arms attached to them (Nezhat 2008, Frumovitz, Escobar et al. 2011).

When all the trocars have been inserted, the patient is placed in the lithotomy/Trendelenburg position, and a depth of 20–30 degrees is selected. The following phases are typical only to robotic-assisted surgery. The first phase is docking, i.e. attaching the robot on the patient using trocars (Nezhat 2008, Frumovitz, Escobar et al. 2011).

1.5.2.2 Docking

Docking means attaching the robot to the patient. The docking time is the time from when the trocars are in place until the console time starts.

The robot can be brought close to the patient either between the legs or from either side of the patient. If the robot is attached on the patient just once, it is called single center docking (SD), and if twice, it is called double docking (DD) (Franké, Narducci et al. 2015).

In gynecology, the operating direction is usually from the upper abdomen towards the pelvis. In this case, the trocars are inserted into the upper abdomen, and the camera and the instruments that are directed towards the pelvis. SD in used in this setup. Sometimes the operating direction has to be reversed, *i.e.* towards the upper abdomen. In this case, the robot has to be de-docked, the patient rotated 180 degrees and the redocked (DD) (Franké, Narducci et al. 2015, Ekdahl, Salehi et al. 2016).

Most gynecologic operations can be performed using the SD technique. In para-aortic lymphadenectomy, the DD technique is used in parallel with the SD technique (Franké, Narducci et al. 2015, Ekdahl, Salehi et al. 2016).

1.5.2.3 Console working

After docking, the surgeon begins the console working. The surgeon sits in front of the console, places his/her fingers on the two console joysticks, looks at the view of the abdominal cavity in the console and starts moving the robotic arms using the joysticks. The surgeon uses the foot pedal to choose which two out of three arms he wants to move. An instrument in one arm can be locked in place to hold tissue, etc. Electrocautery is controlled with foot pedals.

Another surgeon acts as an assistant on the patient's side. 1–2 additional trocars are used by the assistant to insert instruments, such as suction or forceps, into the abdominal cavity, to remove tissue samples or to introduce a needle.

When the console working has been completed, the robot is de-docked (or detached) and the assistant closes the laparoscopic wounds (Nezhat 2008, Frumovitz, Escobar et al. 2011).

1.6 Learning of the robotic-assisted surgery

The surgeon's wrist movements made at the console mimic the wrist movements in open surgery (laparotomy), making robotic-assisted surgery easier to learn than traditional endoscopic surgery. The three-dimensional view facilitates learning because a virtual world can be utilized for learning robotic-assisted surgery. (Abboudi, Khan et al. 2013).

The advantages of robotic-assisted surgery (Table 7) as opposed to conventional laparoscopy have been described in retrospective and observational studies (Liu, Lawrie et al. 2014). Because of these advantages, the learning curve is faster than in conventional laparoscopy (Lim, Kang et al. 2011, Lim, Kang et al. 2010, Seamon, Fowler et al. 2009); e.g. endoscopic suturing technique can be adopted faster (Mettler, Schollmeyer et al. 2008).

The multicenter study of Lowe et al. established the learning curve based on the operation times of several surgeons in 405 staging operations for endometrial carcinoma. The learning curve was found to be short, the fastest adaptation taking place during only the first 9–20 cases (Lowe, Johnson et al. 2009). Likewise, Seamon et al. reported that the learning curve was about 20 cases with pelvic–aortic lymphadenectomy for endometrial cancer patients (Seamon, Fowler et al. 2009).

However, there are studies which observed a noticeably longer learning curve in gynecological operations. Lenihan et al. found the learning curve to be 50 operations in benign gynecology. The study included the 50 first operations of two surgeons, out of which 78% were performed by surgeon A and 22% by surgeon B. They assisted each other in the operations, and the procedures included different types of operation, mainly hysterectomies (Lenihan Jr, Kovanda et al. 2008). In the study of Leitao et al. on patients with endometrial carcinoma, the operation time was found to be longer in robotic-assisted laparoscopy than in traditional laparoscopy during the first 40 operations. After this learning curve for robotic-assisted surgery, there were no significant differences in the operation times (Leitao Jr, Briscoe et al. 2012).

The da Vinci Surgical Skills simulator available for the da Vinci Si (2009) and Xi (2014) models, significantly improves basic robotic surgical skills necessary to operate the da Vinci Si surgical console ($p < .001$) (Gomez, Willis et al. 2015).

1.7 Robotic-assisted lymph node dissection in gynecologic oncology

In gynecology, robotic-assisted surgery has been introduced especially in cancer surgery (Mendivil, Holloway et al. 2009). The most important patient groups have been the ones with endometrial cancer, those that require a staging operation for the confirmation of an apparent early stage ovarian cancer, as well as cervical cancer patients, who would previously have been usually operated on with open surgery (Estape, Estape et al. 2009, Krill, Bristow 2013, Nezhat 2008, Lowe, Johnson et al. 2009).

In endometrial, cervical and ovarian cancer, lymphadenectomy has an important role in surgery. Pelvic and para-aortic lymphadenectomy is necessary to define the extent of the cancer and the possible subsequent treatment (Creasman 2009, Pecorelli, Zigliani et al. 2009, Mutch, Prat 2014). Para-aortic lymphadenectomy (PALND) has been a part of surgical staging in ovarian cancer for 30 years, as FIGO has recommended it since the year 1986 (Angioli, Plotti et al. 2008). Also in endometrial cancer, FIGO recommended a "selected" para-aortic lymphadenectomy already from 1988, but its performance has varied widely.

Para-aortic lymphadenectomy is part of open surgery for advanced ovarian cancer, but for clinically early stage cancer or secondary staging, the robotic-assisted technique is a good technique providing faster recovery (Magrina, Magtibay 2011, Brown, Mendivil et al. 2014). On the other hand, minimal invasive surgery is the treatment of choice for the majority of patients with endometrial cancer, either using traditional or robotic-assisted technique. Although in general no significant differences in the number of pelvic and para-aortic nodes harvested using either technique have been found (Nevis, Vali et al. 2017), especially in obese women para-aortic lymphadenectomy is challenging to perform using the traditional approach, and the number of conversions has been lower in robotic-assisted surgery than in traditional laparoscopic surgery (Gehrig, Cantrell et al. 2008).

1.7.1 Pelvic lymphadenectomy

The purpose of pelvic lymphadenectomy (PLND) is to find out if there are cancer cells in the pelvic lymph nodes. (Mutch, Prat 2014, Mutch 2009, Pecorelli, Zigliani et al. 2009, Pecorelli 2009). Lymph node-fatty tissue is removed from the pelvic area above the external iliac artery and vein on both sides, and from the obturator fossa to reveal the obturator nerve. On the top, pelvic lymph nodes usually extend to the area where the ureter crosses over the common iliac artery. On the medial aspect of the ureter, the lymph nodes continue as para-aortic lymph nodes (Figure 4).

In robotic-assisted and traditional laparoscopy, the surgical techniques for lymphadenectomy are very similar. The main principle of the operation is the same. In robotic-assisted laparoscopy, it is even more important than in traditional technique to see the tips of the instruments at all times because the surgeon cannot feel the tissue when using the console and the operation is based on optical guidance. Some vessel injuries have been described as a complication of lymphadenectomy. The operation involves working right next to large vessels, and if the instrument movement is too strong or careless, it can puncture a hole in a vessel, especially in veins with thin walls that are easily damaged. In most cases of robotic-assisted gynecological operations, damage to blood vessels happens in the area of the external iliac vein (Veljovich 2008, Lowe, Johnson et al. 2009).

1.7.2 Robotic-assisted para-aortic lymphadenectomy

In PALND, lymph nodes are removed from the bifurcation of aorta until the level of the renal veins (Figure 4). PALND is a challenging procedure to perform in endoscopic surgery. When using traditional laparoscopy, the target level is often not reached, but the operation is extended cranially only until the level of IMA. However, in robotic-assisted surgery lymph nodes have been successfully removed up to the level of the renal vein (James, Rakowski et al. 2015, Geppert, Persson et al. 2015, Ekdahl, Salehi et al. 2016).

When robotic-assisted laparoscopy is used for performing PALND, two docking techniques have been used, either single center docking (SD) or double docking (DD). In the SD technique, the robot is docked usually between the legs of the patient, while in DD, two operating directions are used (Franké, Narducci et al. 2015). Two options can also be used to gain access to the para-aortic area, either a transperitoneal or extraperitoneal approach (Wisner, Gupta et al. 2015). In gynecologic surgery, the transperitoneal approach is more common, because PALND is often performed in conjunction with laparoscopy hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymphadenectomy (LH+BSO+PLND) (Iavazzo, Gkegkes 2016).

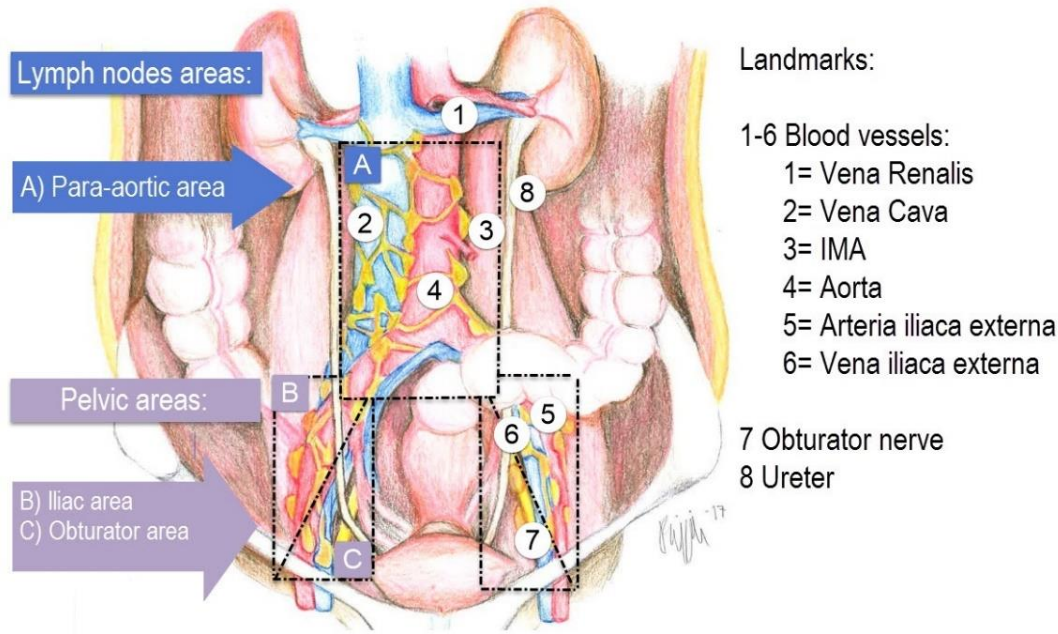


Figure 4. Landmarks of lymph node areas

1.7.2.1 Transperitoneal technique

The advantage of the transperitoneal approach is that all stages of the operation can be done with the SD technique, without moving the robot or trocars. Furthermore, the robotic arms are easier to insert through the abdominal trocars. In the SD technique, the trocars are placed very high. This allows working towards the pelvis. In this case, the targeted renal vein level is directly below the opening of the trocar for the camera (Franké, Narducci et al. 2015, Geppert, Persson et al. 2015, James, Rakowski et al. 2015).

When using the SD technique and transperitoneal approach, the number of pelvic lymph nodes has varied between 18–23 and the number of para-aortic lymph nodes between 10–15 (James, Rakowski et al. 2015, Geppert, Persson et al. 2015). In smaller studies, fewer nodes have been harvested, indicating that a learning curve had probably not yet been established (Lambaudie, Narducci et al. 2012, Pakish, Soliman et al. 2014). A transperitoneal PALND can also be performed using the DD technique, where high numbers of lymph nodes have been reported (pelvic 20, para-aortic 16) (Ekdahl, Salehi et al. 2016). In a small study by Franke et al. (Franké, Narducci et al. 2015), it seemed that the number of para-aortic lymph nodes harvested is higher using the DD technique rather than the SD technique (11 vs. 6).

In the transperitoneal technique, the abdominal cavity is accessed in the normal manner. The abdominal cavity is inspected thoroughly and a cytological specimen is collected. If PALND is planned, it is usually performed at the beginning of the operation after omentectomy when appropriate. Motility of the intestinal tract may impede visibility in the surgical field, and this is usually less disadvantageous at the beginning of the operation. The cecum is mobilized and moved to the upper abdomen, away from the surgical field, to improve visibility. The peritoneum is opened above the para-aortic area, and the lymph nodes removed. The nodal dissection is started from the area of the right common iliac artery, followed by a removal of the lymph nodes from the surface of vena cava and aorta and between them, exposing the vessels up to the level of the right renal vein. After this, the lymph nodes on the left side of the aorta are removed up to the level of the left renal vein, taking care to cause no damage to the IMA. (Köhler, Tozzi et al. 2003).

1.7.2.2 Extraperitoneal technique

The extraperitoneal technique is clearly used more seldom in PALND (Iavazzo, Gkegkes 2016). Procedures involving the free abdominal cavity cannot be included in the operation, and PALND is rarely the only procedure to be performed.

A diagnostic laparoscopy is performed at the beginning of the operation to exclude peritoneal carcinomatosis (Narducci, Lambaudie et al. 2009). The extraperitoneal space is entered bluntly on the left side of the patient the trocars are inserted into the left flank where there is less area for placing the trocars than when using the transperitoneal approach. Care must be taken to avoid entering the abdominal cavity. In the extraperitoneal technique, the arms of the robot can collide more easily, which can prevent their mobility (Hudry, Ahmad et al. 2015). Diaz-Feijoo et al. showed that a 10–15-degree rotation of the table to the right helps to avoid the collision of arms during the extraperitoneal infrarenal dissection. They stated that there are no differences in perioperative outcomes between robotic-assisted and conventional laparoscopic extraperitoneal PALND (Diaz-Feijoo, Gil-Ibanez et al. 2014).

Good lymph node counts have been reported when using extraperitoneal technique. In the following studies, the median of para-aortic lymph nodes was 17, (17 patients) (Diaz-Feijoo, Gil-Ibanez et al. 2014),16.7 (15 patients) (Lambaudie, Narducci et al. 2012), and 18 (24 patients) (Bats, Mimouni et al. 2014), respectively.

Advantages of the extraperitoneal approach include avoidance of ileus, hernia or extreme Trendelenburg position. Technique also reduces the risk for postoperative adhesions. Formation of lymphocysts is a disadvantage of the extraperitoneal technique. These have been reported postoperatively in 19% of cases (Narducci, Lambaudie et al. 2015).

1.7.3 Sentinel lymph node

The objective of sentinel node (SLN) mapping is to find the sentinel lymph node, or the first lymph node downstream from the malignant tumor. The presumption is that if the SLN is clean, metastases are not present in other lymph nodes either. SLN mapping is used to avoid extensive lymphadenectomy. Removal of a large number of lymph nodes may have harmful effects, such as lymphedema, lymphocele formation and prolonged surgical duration (Marin, Pleşca et al. 2014). A combination of blue dye and Tc-99 or indocyanine green (ICG) can be used in SLN mapping.

SLN mapping has been used in gynecologic oncology first for vulvar and cervical cancer (Abdullah, Huang et al. 2013, Kadkhodayan, Hasanzadeh et al. 2014). In endometrial cancer, its use is still at the research stage. According to a meta-analysis of 26 studies, the sensitivity of SLN mapping in detecting lymph node metastasis is 93% in endometrial cancer (Kang, Yoo et al. 2011). However, a new meta-analysis implies that SLN mapping may be the new standard of care in the treatment of endometrial cancer (Smith, Fader et al. 2016).

In robotic-assisted laparoscopy, SLN mapping has been used successfully in patients with endometrial cancer. Indocyanine green dye (ICG) is injected intracervically. The study detected all women with stage IIIC disease. The low false-negative rates were also encouraging (Paley, Veljovich et al. 2016). In robotic-assisted surgery, cervical ICG injection and hysteroscopic injection into the endometrium have been compared in patients with endometrial cancer. This requires the robotic model Si or Xi and Firefly. The detection rate of the SLN was better after cervical injection (Rossi, Jackson et al. 2013). Because of the promising study results, it has also been considered that, in patients with endometrial cancer with low or intermediate risk, SLN biopsy could be used as a compromise between systematic lymphadenectomy and no lymph node biopsy (Ballester, Dubernard et al. 2011).

1.8 Robotic-assisted versus traditional laparoscopic surgery

1.8.1 Endometrial cancer

According to American National Cancer Data Base (2010–2012), MIS is used in 62% of endometrial cancer operations, out of which 77% are performed using robotic-assisted technique (Bregar, Melamed et al. 2017).

Studies comparing robotic-assisted laparoscopy to conventional laparoscopy in the treatment of early stage endometrial cancer are presented in Table 8.

Table 8. Summary of studies comparing robotic-assisted laparoscopy and traditional laparoscopy in the treatment of endometrial cancer (Md = Median, n.d. = no data, PA = para-aortic)

Endometrial cancer		Robotic-assisted laparoscopy							Traditional laparoscopy						
Study	Statistics	n	Age / BMI	Length of operation (min)	Blood loss (mL)	Pelvic/PA nodes	Hospital stay (day)	Conversion/ Complication rate (%)	n	Age / BMI	Length of operation (min)	Blood loss (mL)	Pelvic/ PA nodes	Hospital stay (day)	Conversion/ Complication rate (%)
Veljovich 2008	Md	**25**	60 / 28	283	67	18	1.7	n.d / 20	**4**	54 / 25	255	75	20	1.2	n.d
Bell 2008	Mean	**40**	63 / 33	184	166	17 / n.d	2.3	n.d / 7.5	**30**	68 / 32	171	253	17 / n.d	2	n.d / 20
Boggess 2008	Mean	**103**	62 / 33	191	75	21 / 12	1	2.9 / 5.8	**81**	62 / 29	213	146	17 / 6	1.2	4.9 / 13.6
Gehrig 2008	Mean	**49**	61/ 37.5	189	50	22 / 10	1	0 / 6.5	**32**	61 / 35	215	150	18 / 7	1.3	6.3 / 17.3
Seamon, Cohn 2009	Mean	**105**	59 / 34	242	88	21 / 10	1	12.4 / 13	**76**	57 / 29	287	200	22 / 11	2	26.3 / 14
Hoekstra 2009	Md	**32**	62 / 29	195	50	17	1	3 / 19	**7**	59 / 37	270	150	16	1	29 / 29
Cardenas-Goicoeche a 2010	Md	**102**	61 / 31	222	100	13 / 9	1	1.0 /26.5	**173**	59 / 30	170	100	15 / 6	2	5.2 / 31.8
Lim 2010	Mean	**56**	63 /30	163	89	19 / 13	1.6	1.8 / 14.3	**56**	61 / 28	192	209	24 / 21	2.6	7.1 / 21.4
Jung 2010	Mean	**28**	53 / 23	193	n.d	21 / 8	8	0 /7.1	**25**	50 / 25	165	n.d	18 / 4	8	0 / 8.0
Magrina 2011	Mean	**67**	n.d	182	141	25	1.9	2.9/	**37**	n.d	190	301	27	3.4	10.8 /
Lim 2011	Mean	**122**	62 / 31	147	81	19 / 6	1.5	0.8 /10.7	**122**	62 / 30	187	207	25 / 18	3.2	6.5 /19.7
Martino 2011	Mean	**101**	62 / 35	n.d	n.d	14 / 5	n.d	n.d	**114**	64 / 34	n.d	n.d	12 / 5	n.d	n.d
Coronado 2012	Mean	**71**	67 /29	189	99	16 / 6	3.5	2.4 / 21.1	**84**	66 / 27	218	190	18 /6	4.6	8.1 / 28.5

Wright 2012		**1437**	n.d	n.d	n.d	n.d	n.d	/ 8.1	**1027**	n.d	n.d	n.d	n.d	n.d	/ 9.8
Leitao 2012	Md	**347**	60 / 29	213	50	13 / 6	1	11 / 10	**302**	62 / 28	184	100	15 / 5	2	13 /14
Cardenas-Goicoechea 2013	Md	**183**	62 / 29	n.d	n.d	13 / 8	n.d	n.d	**232**	61 / 29	n.d	n.d	15 / 7	n.d	n.d
Turunen 2013	Mean	**67**	65 / 28	218	50	17	n.d	0 / 12	**150**	67 / 29	138	100	17	n.d	3.3 / 15
Chiou 2015	Md	**86**	53 / 26	145	50	26	3	0 / 2.3	**150**	51 / 25	173	100	22	3	0 / 1.3
Corrado 2015	Md	**72**	63 /29	115	100	16 / 6	3	1.4 /5.6	**277**	62 / 29	100	100	12 / 9	4	5.4 /10.1

The majority of studies have found that operation time is longer in robotic-assisted laparoscopy than in traditional laparoscopy, but not universally (Corrado, Cutillo et al. 2015, Seror, Bats et al. 2014, Manchana, Puangsricharoen et al. 2015, Bell, Torgerson et al. 2008, Cardenas-Goicoechea, Adams et al. 2010).

Lönnerfors et al. have conducted a randomized study on hysterectomies performed for benign indications, comparing traditional mini-invasive surgery and robotic-assisted surgery. No significant difference in operation time was noticed between these techniques. For traditional surgery, the surgeon selected either vaginal or laparoscopic surgical technique (Lönnerfors, Reynisson et al. 2015). Two other randomized studies have also been conducted on hysterectomies performed for benign indications that compared traditional mini-invasive surgery and robotic-assisted surgery. They found that robotic-assisted surgery took longer to perform (Sarlos, Kots et al. 2012, Paraiso, Ridgeway et al. 2013).

The EBL has been lower in robotic-assisted laparoscopy compared to traditional laparoscopy, and the amount of bleeding is usually very small in the operations, approximately between 10–120 mL, and often does not have clinical significance. In most studies, there was also no significant difference between the number of removed lymph nodes, complications, or time of discharge (Minig, Achilarre et al. 2017).

Length of hospital stay following robotic-assisted laparoscopy is generally 1–2 days, and some studies have found it to be shorter than after traditional laparoscopy (Cardenas-Goicoechea, Soto et al. 2012, Lim, Kang et al. 2011, Seamon, Cohn et al. 2009, Boggess 2008).

Comparative studies have found a smaller number of conversions to open operations as an advantage of robotic-assisted surgery (Cardenas-Goicoechea, Soto et al. 2012, Corrado, Cutillo et al. 2015, Lim, Kang et al. 2011, Seamon, Cohn et al. 2009). This is very important, because recovery is significantly slower after laparotomy, and it is associated with much longer hospital stays, delay in the beginning on the adjuvant therapy, more complications and higher costs (Malur, Possover et al. 2001, Gemignani, Curtin et al. 1999). The number of conversions (0-12%) is especially low in obese patients when robotic-assisted surgery is used (Lim, Kang et al. 2011, Seamon, Cohn et al. 2009, Gehrig, Cantrell et al. 2008).

A review of eight large studies by Gaia et al. assessed 589 patients that had undergone robotic-assisted surgery and 396 patients traditional laparoscopy and found that patients undergoing robotic-assisted surgery had less EBL, 92 vs. 182 ml ($p = 0.001$). There was no significant difference in operation time, number of lymph nodes or complications. The same is true for conversions (robotic 4.9% and laparoscopic 9.9%, p = 0.06) (Gaia, Holloway et al. 2010).

No difference in 3-year survival and recurrence has been found between the robotic-assisted and traditional laparoscopic techniques (Cardenas-Goicoechea, Shepherd et al. 2013, Corrado, Cutillo et al. 2015, Coronado, Herraiz et al. 2012). The study by Chiou et al. reported a similar result after 18-month follow-up (Chiou, Chiu et al. 2015).

1.8.2 Cervical cancer

In 2008, Fanning et al. published the surgical outcomes of the first 20 patients with early stage cervical cancer operated by aid of the robotic-assisted laparoscopy. All 20 operations were successful, median EBL was 300 ml, the number of complications was minimal and all patients were discharged on the first postoperative day. The median operation time was 6.5h (range 3.5–8.5) (Fanning, Fenton et al. 2008). They found that the incidence of complications was 10%, i.e. less than half compared to earlier laparoscopic studies of cervical cancer (19–29%) (Abu-Rustum, Gemignani et al. 2003, Spirtos, Eisenkop et al. 2002, Nezhat, Mahdavi et al. 2006).

Shazly et al. performed an extensive meta-analysis of 26 non-randomized studies on the use of laparoscopic, robotic-assisted and open surgical techniques in stage IA1–IIA cervical carcinoma (n=4013). The robotic-assisted technique was associated with less EBL and complications as well as shorter hospital stay. Laparoscopic and robotic-assisted surgery gave similar results with regard to intraoperative complications and short-term postoperative outcomes (Shazly, Murad et al. 2015).

Similarly, as in patients with endometrial carcinoma, contradicting results have been observed in patients with cervical cancer when comparing which technique, robotic-assisted or traditional laparoscopy, is faster (Minig, Achilarre et al. 2017). Robotic-assisted laparoscopy has been found to be both slower: 173 min vs. 107 min; $p < 0.001$ (Mendivil, Rettenmaier et al. 2016), 230 vs. 211 min; $p = 0.025$ (Chong, Lee et al. 2013) and faster: 193 vs. 293 min; $p < 0.05$ (Chen, Chiu et al. 2014), 263 vs. 364 min; $p < 0.001$ (Sert, Abeler 2011) than traditional laparoscopy in terms of operation time.

Because traditional laparoscopic surgery is challenging, cervical carcinoma has been operated on with traditional laparotomy in several hospitals, and that has been the standard care. A case control study of Maggioni et al. compared robotic-assisted surgery with laparotomy and found that EBL was significantly lower (78 vs. 222ml, $p< .0001$), hospital stays were shorter (3.7 vs. 5.0, $p<0.01$) and the robotic-assisted procedures were safe (Maggioni, Minig et al. 2009).

In early-stage cervical carcinoma, the first results between robotic-assisted and traditional laparoscopy were published in 2007. Robotic-assisted operations were started without problems, and the histopathological results did not differ from traditional laparoscopy; the parametrial tissue, vaginal cuff size and the number of lymph nodes were similar in both groups (Sert, Abeler 2007). The 5-year survival outcomes were compared between patients with cervical cancer who underwent an open radical hysterectomy (ORH), robotic-assisted radical hysterectomy (RRH) or laparoscopic radical hysterectomy (LRH) for the treatment of their disease. The groups had similar 5-year disease-free and overall survival outcomes (Estape, Estape et al. 2009).

During radical hysterectomy, the amount of intraoperative bleeding was usually higher than during traditional hysterectomy. EBL has been found to be smaller when using the robotic-assisted technique than when using traditional laparoscopy: 82 vs. 164 ml; $p< 0.001$ (Sert, Abeler 2011), 55 vs. 202 ml; $p< 0.001$ (Chong, Lee et al. 2013), 71 vs. 160 ml; $p=0.038$ (Sert, Abeler 2007), 100 vs. 145 ml; $p=0.037$ (Yim, Kim et al. 2015), 75 vs. 150 ml; $p<0.05$ (Chen, Chiu et al. 2014).

A retrospective multi-center study, which included patients with early-stage cervical cancer (n=99), assessed safety of the operation, complications and recurrence in traditional (LRH) and robotic-assisted (RRH) laparoscopy. Both operations included lymphadenectomy, and no significant difference was found in the outcomes between the groups (Tinelli, Malzoni et al. 2011). In the study of Yim et al., postoperative complication rates were lower in the robotic group, 17% vs. 31%, $p=0.028$. (Yim, Kim et al. 2014) The same is true for the study of Estape et al., 18.8% vs. 23.5% (Estape, Estape et al. 2009). The length of hospital stay was longer in traditional laparoscopy (Sert, Abeler 2011, Magrina, Zanagnolo 2008). There were no significant differences in length, however in the study of Chen et al. (Chen, Chiu et al. 2014).

In several studies, more lymph nodes could be removed when using the robotic-assisted technique compared to traditional laparoscopy: 19.5 (± 6.9) vs. 15.4 (± 8.4) nodes; $p = 0.388$ (Sert, Abeler 2011), 32 vs. 19, $p< 0.0001$ (Estape, Estape et al. 2009) and 15 vs. 11, $p=0.005$ (Mendivil, Rettenmaier et al. 2016) Some studies did not find any difference between the number of lymph nodes (Chong, Lee et al. 2013) and 23 (±9.3) vs. 22 (±9.8), $p=0.248$ (Yim, Kim et al. 2014).

In radical hysterectomy following NACT, EBL was found to be significantly smaller in the robotic-assisted laparoscopy group (n=25) than in the traditional laparoscopy group (n=25), 160 (range 50–580) vs. 220 (range 30–480) ml; $p<0.001$. Operation time was almost the same, 190 (range 105–300) vs. 188 (range 140–280) min. (Vizza, Corrado et al. 2015).

In their large retrospective study, Api et al. compared radical trachelectomy in robotic-assisted (n=45) and traditional laparoscopic technique (n=216). robotic-assisted surgery was associated with slightly longer operation times (308 vs. 296 min, $p<0.001$), shorter hospital stays (1.5 vs. 9, $p<0.001$) and smaller EBL (62 vs. 185, $p<0.001$), but with a smaller number of pelvic lymph nodes (22 vs. 32, $p=0.02$). There was no difference between postoperative pregnancies or oncologic outcomes (Api, Boza et al. 2016).

1.8.3 Ovarian cancer

A few comparative studies have been conducted on staging operations in early-stage ovarian cancer. When comparing the robotic-assisted and traditional techniques, there was no significant difference in the number of removed pelvic or para-aortic lymph nodes or oncological outcomes, and survival did not change significantly in relation to the type of surgery (Magrina, Zanagnolo et al. 2011, Nezhat, Finger et al. 2014, Chen, Chiu et al. 2015).

In one study out of three, operation time tended to be shorter in the robotic group, but the difference was not significant (Chen, Chiu et al. 2015), while in one study it was significantly longer (Magrina, Zanagnolo et al. 2011). In the study of Magrina et al., a significant difference ($p<0.001$) between the groups was seen in postoperative complications, the rate of which was 24% in the robotic group and only 4% in the traditional laparoscopy group. However, median intraoperative bleeding was smaller in the robotic group, 100 (range 10–450) vs. 150 (10–1400) ml, ($p<0.001$) (Magrina, Zanagnolo et al. 2011).

1.9 Costs of robotic-assisted laparoscopy

Robotic-assisted surgery is generally considered to be expensive. According to the American Perspective database from 2008 to 2010, the mean cost of the robotic-assisted hysterectomy vs. the traditional laparoscopic hysterectomy for endometrial cancer was $10,618 vs. $8,996, respectively ($p < 0.001$), while morbidity was similar ($p = 0.13$) (Wright, Burke et al. 2012). However, a cost-effectiveness analysis of robotic-assisted surgery found that total costs without equipment are comparable to traditional laparoscopy, and lower than in open operations (USD 20,289, USD 20,467 and USD 24,433, respectively) for newly diagnosed uterine cancers (Leitao, Bartashnik et al. 2014). The study of Barnett et al. (2010) used three separate models with sensitivity analysis to assess the costs of surgical techniques used to treat endometrial carcinoma. Laparoscopy was assessed to be the least expensive and open operations the most expensive. In open operations, longer recoveries increase the costs borne by the society. Robotic-assisted surgery was predicted to be the least expensive technique, if the prices of single-use robotic instruments would decrease per operation (from USD 2394 to USD 1496) (Barnett, Judd et al. 2010). Bell et al. assessed that open surgeries are significantly more expensive than robotic-assisted surgeries also in the treatment of endometrial carcinoma, despite the fact that robotic-assisted surgeries lasted 76 minutes longer and the difference in the length of hospital stay was only 1.7 days (Bell, Torgerson et al. 2008).

In the study of Scalici et al., a statistically significant difference was found between the MIS and open surgery groups in the complication rate, 12 vs. 31%, $p < 0.001$. They calculated healthcare costs in USD, on the level of 2014, making the median cost of a hospital day USD 4,350. In the cohort of the study of Scalici et al. (n=2076), each 10% increase in the use of MIS would decrease the number of postoperative complications by 41 and the number of hospital days by 600. It would also decrease the costs incurred by treatment of complications in this group by USD 2.8 million. If all patients would have been treated with MIS, there would have been 416 complications and 6,434 hospital days fewer, and USD 27 million would have been saved per year. They speculated a scenario where MIS would be used in 90% of patients with endometrial carcinoma in the USA. The result would be 8,059 complications fewer and 127,251 hospital days fewer, which would in turn generate savings of USD 534 million per year compared to open surgery (Scalici, Laughlin et al. 2014).

Wright et al. analyzed the costs of robotic-assisted and traditional laparoscopy related to hysterectomy for benign and malignant indications. In benign indications, the median cost of robotic-assisted surgery was USD 8,152 and the median cost of traditional laparoscopy USD 6,535 ($p < .001$). For endometrial cancer patients, it was USD 9,691 vs. USD 8,237, respectively ($p < .001$). The cost difference between robotic-assisted surgery and traditional laparoscopy decreased when more procedures were performed (Wright, Ananth et al. 2014).

The costs of robotic-assisted laparoscopy have also been studied in the surgery for cervical cancer. Robotic-assisted surgery was found to be less expensive than open operation by Halliday et al., even when the amortization costs of the robot were included (Halliday, Lau et al. 2010b). On the contrary, Reynisson and Persson reported higher costs of robotic-assisted surgery compared to open operations, but only during the first 90 operations. There was no cost difference after the learning curve (Reynisson, Persson et al. 2013). Wright et al. also achieve similar results with regard to open surgery and the robotic-assisted and traditional laparoscopic techniques. Open surgery was the least expensive (USD 9,618), followed by robotic-assisted laparoscopy (USD 10,176) and the most expensive option, traditional laparoscopy (USD 11,774) (Wright, Herzog et al. 2012). On the contrary, Desille-Gbaguidi et al. found that robotic-assisted radical hysterectomy was significantly more expensive than traditional laparoscopic surgery. Overall average care cost was EUR 7,803 for the laparoscopic group (with an average length of stay of 5.83 days) as compared to EUR 12,211 for the robotic group (with an average hospital stay of 4.70 days) $p= 0.07$. They achieved the same result for endometrial carcinoma. Overall, the average cost for patient treatment was EUR 6,666 for the laparoscopic group (with an average length of stay of 5.27 days) as compared to EUR 10,816 for the robotic group (with an average hospital stay of 4.60 days), $p = 0.39$ (Desille-Gbaguidi, Hebert et al. 2013).

1.10 Robotic-assisted surgery in Finland

In Finland, robotic-assisted operations were started 9 years ago, in December 2008 in Tampere. The first operation was a prostatectomy performed by urologists. On 24 March 2009, the first gynecologic robotic-assisted laparoscopy operation was performed in Tampere, or hysterectomy, BSO and PLND on a patient with endometrial carcinoma. Since then, more than 700 gynecological patients have been operated on, mainly due to cancer. The most recent step forward has been the acquisition of the newest da Vinci Model or Xi on 31 October 2017.

Gynecologic robotic-assisted operations were started in Helsinki in 2009, in Turku in 2010, in Oulu in 2011 and in Kuopio in 2016.

In Finland, gynecological operations have concentrated so far on cancer patients, and only individual patients have been operated on for benign indications. This is partly explained by the Finnish HALO overview that recommended robotic-assisted surgery only for operations on cancer patients (Tapper, Hannola et al. 2014).

2 AIMS OF THE STUDY

The present study was undertaken to investigate the usefulness of the robotic-assisted technique in the surgery for gynecological cancer. The specific aims of the study were:

1. To investigate the initial experience and learning curve with robotic-assisted laparoscopic surgery in gynecologic oncology.

2. To prospectively compare traditional and robotic-assisted laparoscopic surgery for endometrial cancer in a randomized, controlled trial.

3. To compare the costs of traditional laparoscopy and robotic-assisted laparoscopy in the treatment of endometrial cancer.

4. To investigate the technical and surgical outcomes and learning curve of robotic-assisted para-aortic lymphadenectomy.

3 MATERIALS AND METHODS

All robotic-assisted and traditional laparoscopic operations referred in this Thesis were performed at the Department of Obstetrics and Gynecology of Tampere University Hospital. The data set was founded on 24 March 2009, when the first gynecologic robotic-assisted laparoscopic surgery was performed. Data on robotic-assisted surgeries was collected until 26 September 2016. By that time, 646 gynecological patients had undergone robotic-assisted surgery. As a rule, two operations per week were performed, and the annual rate of the operations was approximately 85 operations.

For the operations, the da Vinci S robotic model (da Vinci S Surgical System, Intuitive Surgical Inc., Sunnyvale, CA) with a single center-docking between the patient legs was used. Robotic-assisted operations were performed in the OR of Coxa hospital where the robot is placed. Traditional laparoscopy operations were performed at the gynecological surgical unit of the Department of Gynecology and Obstetrics of Tampere University Hospital.

Five surgeons performed the traditional laparoscopies, while six surgeons performed the robotic-assisted surgeries: In study I-III, the operations were all performed by three gynecologic surgeons. Two surgeons (A, B) started the operations and a third (C) one joined the team after the first hundred operations. For study IV, material was collected for seven years. During the study period, five gynecologic surgeons performed all robotic-assisted operations: after 300 operations, surgeon B stopped console work and was followed by a fourth surgeon (D), who had already assisted for a longer period of time. The fifth surgeon to start was surgeon (E) who had previously worked as a robotic surgeon at another hospital. When surgeon A stopped console work, sixth surgeon (F) who had only assisted previously, joined the robot team. The nursing team consisted of three qualified OR nurses, who alternated as instrument, anesthetic and passer nurses, respectively. In studies I–IV, the number of nurses and their tasks in OR remained the same but a few new nurses were trained for the robotic team. The total number of nurses was eventually ten. There were several anesthesia doctors but a few of them worked more regularly.

3.1 Study population (I–IV)

All patients undergoing a robotic-assisted operation were consecutive enrolled in the study I. Study II included 101 patients with endometrial carcinoma that were randomized for a robotic-assisted surgery or a traditional laparoscopic surgery. 99 of the randomized patients were eligible for analysis. Study III included the same 99 patients as Study II. Study IV data included all patients with gynecological cancer patients that underwent a robotic-assisted surgery including a PALND procedure. The most common indication for PALND was endometrial cancer (deep myometrial invasion or poor differentiation) (n=239, of which endometrioid type n=175), and the most common operation type (n=160) was laparoscopic hysterectomy, bilateral salpingo-oophorectomy pelvic and para-aortic lymphadenectomy (LH+BSO+PLND+PALND). (Table 9)

Table 9. Study population, design and main outcome in Studies I-IV

Study	Number of patients*	Design	Age (years) Md (range)	BMI Md (range)	Characteristics of study	Main outcome measure	The operations period and follow-up time of 6 months
I	300	Retrospective	62 (20-88)	28 (17-77)	The results on first 300 robotic-assisted operations. Implementing robotic-assisted surgery to gynecologic surgery.	The learning curve events	24-MAR-2009-15-JAN-2013
II	99	Prospective	68 (43-84)	29 (20-46)	Comparison of traditional and robotic-assisted laparoscopic surgery for endometrial cancer.	The overall operation time	20-NOV-2010-15-OCT-2013
III	99	Cohort Study	68 (43-84)	29 (20-46)	Review of Study II patient data with regard to costs.	The true costs	20-NOV-2010-15-OCT-2013
IV	283	Retrospective	67 (23-88)	28 (19-48)	The success of robotic-assisted PALND.	The PALND extent of the operation in terms of the height	29-SEP-2009-27-SEP-2016

* An individual patient may be included in several studies

3.2 Methods

A form was filled in in the OR for all gynecological patients that underwent a robotic-assisted laparoscopy, beginning from the start of robot operations. The lengths of the stages of surgery and operation difficulty levels were recorded on the form. In addition to the form, the patient data for Studies I and IV were gathered later from patient record entries.

Study II information was recorded on forms during treatment planning visits, operations, post-operatively in the ward, during the postoperative tumor boards and at outpatient clinic visits (at 6 months, 1 year, 2 years and 3 years). The information was supplemented with patient record entries. Study III was based on the data of Study II. In addition, cost-related information was gathered from Hospital Management Information System.

3.2.1 Study I

In OR, a nurse recorded the stages of the robotic-assisted surgery and their starting and ending times. An entry was made at the following stages: (1) patient arrived in the OR, (2) start of procedure, (3) skin incision, (4) trocars in place, (5) console work started and (4) ended, (5) closure of incision and (6) patient discharged from OR. The aim was to evaluate the duration of the different stages and the impact that learning had on those durations. The stages were divided as follows in Table 10.

Table 10. Stages of the robotic-assisted surgery in OR

Stages of the robotic-assisted surgery	Description
Preparation time	The time that elapsed from the arrival of the patient to the OR until the start of the operation
Set-up time	The time that elapsed from the start of the operation until the startup of the robotic console, including docking time
Docking time	The time it took to attach the robot and the instruments on the patient
Console time	The time that the surgeon used in the console to operate
OR time	The time that elapsed from the arrival of the patient to the OR until the patient left the OR
Skin to skin time (operation time)	The time that elapsed from the first skin incision to closure

The primary outcome measure was the learning curve events: preparation time, docking time and overall operation time, respectively, which were calculated for each operation. The learning curves were constructed separately for the different surgeons and for the different types of operation.

The secondary outcome measures included the amount of bleeding, intraoperative complications and conversions, as well as the length of postoperative stay, and the number of lymph nodes harvested.

3.2.2 Study II

The inclusion criteria for the study were a low-grade (Grade 1–2) endometrial carcinoma, with planned laparoscopic surgical staging: a LH with BSO and PLND. The exclusion criteria included a narrow vagina or a uterus too large to be removed through the vagina or patients that were estimated not to tolerate a deep Trendelenburg position.

The patients were randomized 1:1 into two arms, traditional or robotic-assisted laparoscopic surgery (Figure 5). The patients were stratified based on age and weight into groups: no overweight / overweight (BMI<30 and ≥30) and age (<65 and ≥65 years). Randomization was performed with minimization software for allocating patients to treatments in clinical trials (MINIM version 1.5/28-3-90) by S. Evans, P. Royston and S. Day (https://www-users.york.ac.uk/~mb55/guide/minim.htm).

The key characteristics in the respective treatment arms include: In the robotic group, the abdominal cavity was accessed through open approach, as contrasted to Veress needle technique in the traditional group. In the traditional group, a reusable uterus manipulator was used, and the uterus was removed by dividing the parametrium vaginally and suturing bottom of the vagina through the vagina. In the robotic group, a single-use uterus manipulator was used. The entire uterus was removed laparoscopically and the vaginal cuff was sutured laparoscopically.

The primary outcome measure was overall operation time. The study was powered to show at least a 25% difference in the operation time using two-sided significance level of 0.05. For this, at least 45 patients were needed in each treatment arm to achieve a power of 0.80.

The secondary outcome measures included the total time spent in the OR, the number of lymph nodes harvested, complications and conversions, the amount of bleeding, the length of postoperative stay, and the postoperative pain scale.

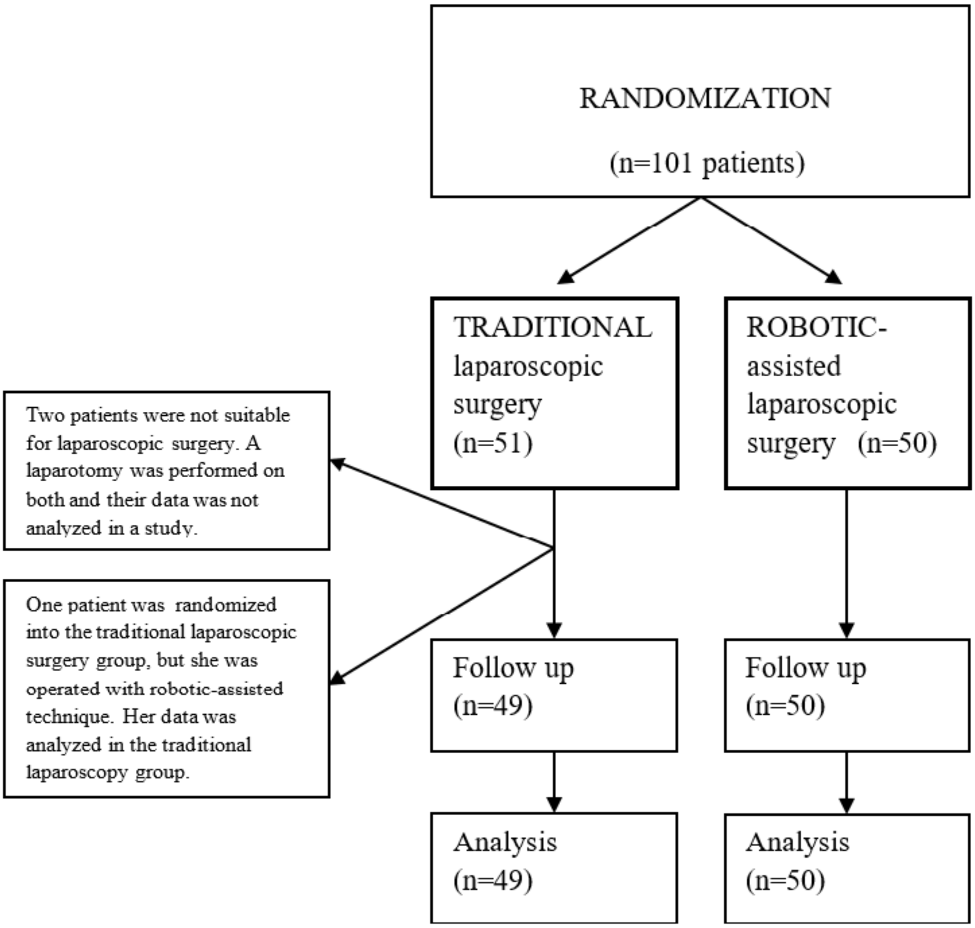


Figure 5. Flow chart

3.2.3 Study III

The hospital databases were searched to find out the actual costs for each patient, during the surgery and post-operatively. The cost variables are presented in Table 11. The costs of purchased services, such as expertise, e.g. anesthetic services, OR services, laboratory services and consultations provided by other specialties like urologic surgery were taken into account. In the calculations, the prices for year 2012 were used, which was the mid-point of the study.

The patient data were collected during the operations and 6 months after the operations, according to the study protocol for Study II. All extra visits and procedures related to recovery were counted towards the complication costs. The complication costs included treatment at the Tampere University Hospital and treatment at the other hospitals responsible for follow-up monitoring. All visits and examinations were included in the costs regardless of whether they were related to a complication or a "normal" post-operative symptom.

The robot at Tampere University Hospital is the Da Vinci® S surgical system (Intuitive Surgical, Inc., Sunnyvale CA). It is a leased product with a 10-year contract. The annual leasing and maintenance costs are EUR 196,000 and EUR 140,000, respectively. These costs were divided by the total number of operations during the year 2012 to calculate the robot platform amortization cost per robot operation.

Main outcome measures were the true costs of traditional laparoscopy and robotic-assisted laparoscopy in endometrial cancer, as calculated on the basis of Study II patient population. Total costs included also the six-month postoperative follow-up.

Table 11. Variable definitions

Variables	Both groups	Traditional	Robot	Comment
Instruments	Disposable instruments and materials, maintenance costs for reusable instruments, OR supplies hemostatic matrix if used	Energy instrument costs	Instrument cost per operation (four basic instruments)	
Inpatient stay	Room and board, ward personnel, ward basic medication			
Lab	Based on the needed studies during operation and inpatient stay			
Radiology	Based on the needed imaging studies during operation and inpatient stay			
Blood products	Blood transfusions and lab samples related to preparation or transfusions			
Operation personnel	0.5 anesthesiologist, 3.25 OR nurses for each operation			Related to OR time
Equipment and OR	Costs of running the OR and the fixed equipment	Amortization of a basic laparoscopy tower	Amortization of the robot console	Related to OR time
General costs	Administrative costs, costs that cannot be calculated elsewhere			Related to OR time
Operation medication	Anesthesia costs and local anesthetics			Related to OR time
Surgeon costs	Two operating specialists			Related to operation time
PACU costs	0.3 nurses per patient and facilities			Related to PACU time
Complications	Additional clinical visits, readmissions, radiology			

3.2.4 Study IV

The operations were performed by five surgeons, three of whom performed the most operations. All used basically similar technique: open access to the abdominal cavity and a 12 mm balloon trocar (trocar 1) to the upper abdomen, at least 10 cm above the umbilicus, CO_2 insufflation and rest trocars in order of the setting (Figure 6): two robotic trocars (2 and 3) were placed to the right upper abdomen, and one robotic trocar (4) to the left upper abdomen. One 5 mm trocar (5) was placed to the left upper abdomen, as well as one 12 mm trocar (6), to the left lower abdomen for the assistant surgeon.

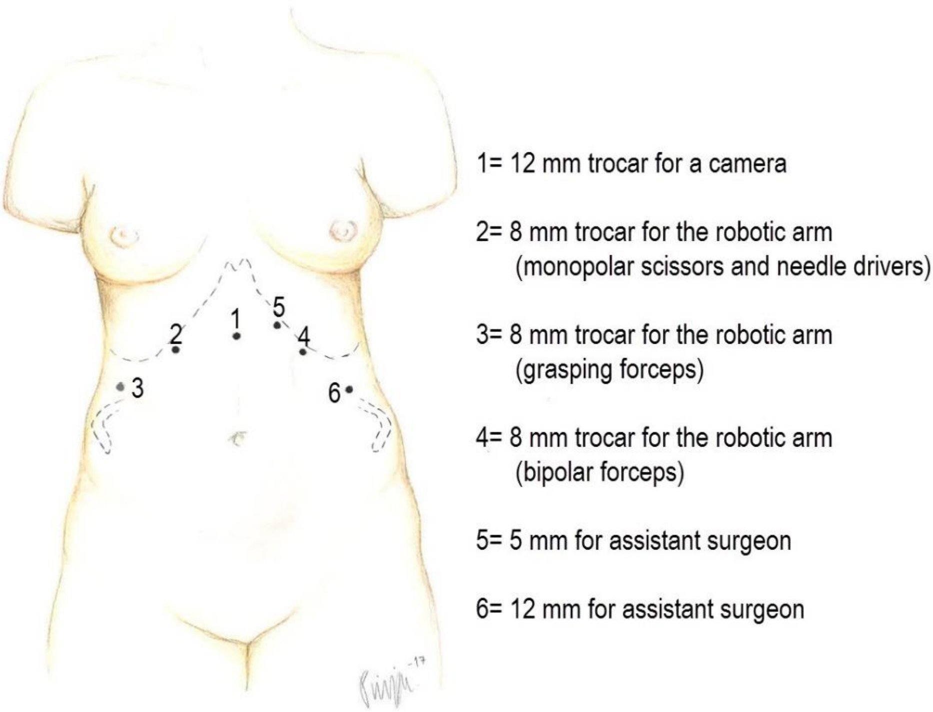


Figure 6. The trocars places in study IV

After placing the trocars, the patient was tilted to a deep, 28-degree Trendelenburg position. Robot docking between the legs (SD), the instruments and the 0-degree scope were placed in the robot arms (Study IV, Materials and Methods).

In the abdominal cavity, the steps were carried out systematically and consistently, following the same pattern each time, and they were recorded in the operation report. First, a cytological specimen was collected. In case removal of the omentum was planned, that was performed first. The cecum was mobilized and the peritoneum covering the para-aortic area was opened. Lymph nodes were removed and the surgeon assessed the level of the lymphadenectomy. The next step was usually the removal of lymph nodes from the pelvic region, followed by the rest of the procedures.

After performing the PALND, the surgeon evaluated up to what level the procedure was successful. A pair of scissors with 7 mm blades was used for the evaluation. Above the IMA, the surgeon assessed the level of progress every 1 cm or, occasionally, every 0.5 cm. The final results were given in full centimeters, and half of the 0.5 cm evaluations were rounded up to the nearest centimeter and the other half rounded down. The maximum height was defined as the level of the renal vein or at least 4 cm cranial to IMA.

The primary outcome measure was the extent of the operation in terms of the height (from the aortic bifurcation to the level of IMA, and up to the renal vessels). By definition, a high level meant extension of the LND cranial to the level of IMA, while the level of the renal veins was maximum level reached.

The secondary outcome measures included operation time and surgical outcome in terms of the number of lymph nodes harvested, the number of metastatic nodes, complications, and recovery.

3.3 Statistical analysis

Study I: Distributions of time values were shown by medians with interquartile ranges and/or ranges. Differences between first and last operations were tested by Mann-Whitney test. Statistical analyses were performed by IBM SPSS Statistics version 20 (IBM Corp., Armonk, NY, USA). The p-values < 0.05 were considered as statistically significant. The term moving average used in three figures of Study I refers to the simple average of operation time over a defined number of time periods to smooth out short-term fluctuations.

Study II: The differences between the traditional laparoscopy and the robotic-assisted surgery groups were tested by Pearson chi-square test, Fisher's exact test or by Mann-Whitney test and/or independent samples t-test. The statistical analyses were performed using IBM SPSS Statistics version 23 (IBM Corp., Armonk, NY, USA). The *p*-values under 0.05 were considered to be statistically significant.

Study III: Distributions of cost factors were shown by medians with interquartile ranges due to the skewed distributions and outliers. Differences between traditional and robotic-assisted laparoscopic surgical costs were analyzed by non-parametric independent-samples Mann-Whitney U test. Categorical variables were tested by Pearson chi-square test or by Fisher's exact test if expected values were too small. Statistical analyses were performed by IBM SPSS Statistics version 23 (IBM Corp., Armonk, NY). The *p*-values less than 0.05 were considered as statistically significant.

Study IV: Categorical values were shown by number of cases with percentages and tested by Pearson chi-square test or by Fisher's exact test if assumption of Pearson chi-square test was not valid. Due to the skewness, continuous distributions were shown by medians (Md) with interquartile ranges (IQR) and/or ranges. Linear associations between continuous variables were analyzed by Spearman's non-parametric correlation coefficient rho. Differences between independent groups were tested by Mann-Whitney test. Dependent measurements were tested by Wilcoxon test. All statistical analyses were performed using IBM SPSS Statistics version 23 (IBM SPSS Statistics, IBM Corporation, Chicago, IL). The p-values < 0.05 were considered as statistically significant.

3.4 Ethical considerations

All sub-studies were approved by the Ethics Committee of Tampere University Hospital. The identification number of Study I was ETL R13157, of studies II–III ETL R10081 and of study IV ETL R16186. Study II was registered at ClinicalTrials.gov, www.clinicaltrials.gov (NCT 01466777).

In Study II, a written informed consent was obtained from the study participants. The same informed consent was applicable to Study III. In Studies I and IV, no informed consent was obtained from the patients, because these were retrospective patient chart reviews, and no identifiable data on the individual patients appear in this Thesis.

4 RESULTS

4.1 Study I: Learning curve

In 242 patients (80.7%), the indication for surgery was a gynecological cancer, and 58 patients (19.3%) had borderline or benign indications. The final histopathological findings of the patients' diseases are presented in Table 12, and the performed procedures in the Original Communication I, Table 1.

Table 12. The final histopathological findings of the patients' diseases in Study I

		Stage								
Indication		IA	I B	I C	II	III A	III B	III C		IV
	Total 300 (100%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n	(%)	n (%)
Endometrial cancer								IIIC1	IIIC2	
Endometrioid	150 (50.0)	79 (52.7)	44 (29.3)		11 (7.3)	4 (2.7)		5 (3.3)	6 (4.0)	1 (0.7)
Serous	26 (8.7)	8 (30.8)	4 (15.4)		4 (15.4)	3 (11.5)	2 (7.7)	3 (11.5)	2 (7.7)	
Other#	8 (2.7)	3 (37.5)	1 (12.5)		2 (25.0)			1 (12.5)	1 (12.5)	
Sarcoma	12 (4.0)	7 (58.3)			3 (30.0)	1 (8.3)			1 (8.3)	
Ovarian and tubal carcinoma										
Serous##	9 (3.0)			2 (22.2)			3 (30.0)	4 (44.4)		
Endometrioid	2 (0.7)	1 (50.0)					1 (50.0)			
Mucinous	5 (1.7)	4 (80.0)		1 (20.0)						
Carcinoma of the uterine cervix	30 (10.0)	6 (20.0)	IB1:23 (76.7)		IIA:1 (3.3)					
Borderline tumour of the ovary	6 (2.0)									
Endometriosis	10 (3.3)									
Myoma	24 (8.0)									
Other*	18 (6.0)									

2 adeno-squamous carcinomas, 3 clear cell carcinomas, 3 mixed cell carcinomas
includes 1 peritoneal carcinosis
* 8 endometrial hyperplasias, 4 pelvic organ prolapse, 4 operations for transgender, 1 cytological atypia, 1 cervical cerclage

4.1.1 Preparation, set-up, docking, operation and operation room times

In robotic-assisted laparoscopy, learning shortened both the OR time and the procedure time. The OR time decreased because the operation time as well as the preparation time decreased. In addition, time needed to learn the operations was short, which is evident from the steep learning curve.

In the first 300 robotic-assisted operations, the median preparation time was 42 minutes (range 18–92). The preparation time was significantly shorter ($p < 0.001$) for the last fifty patients than for the first fifty patients [36 minutes (range 19–54) vs. 58 (range 37–92) minutes, respectively] (Figure 7).

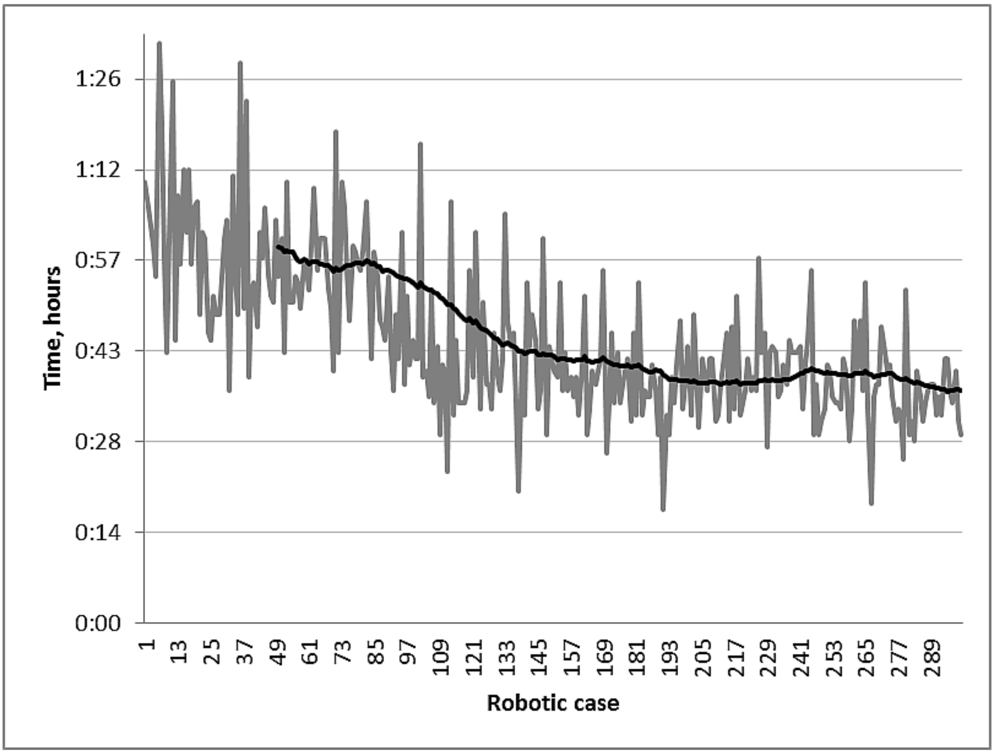


Figure 7. The preparation time with moving average of 50 patients

However, no significant decrease was seen in the next stage, Set-up time of the operation (Figure 8), the median of which was 25 minutes (range 14–98). During this stage, the manipulator was placed in the uterus when appropriate, trocars were placed in the abdomen, the robot was docked and the instruments were attached to the robot arms.

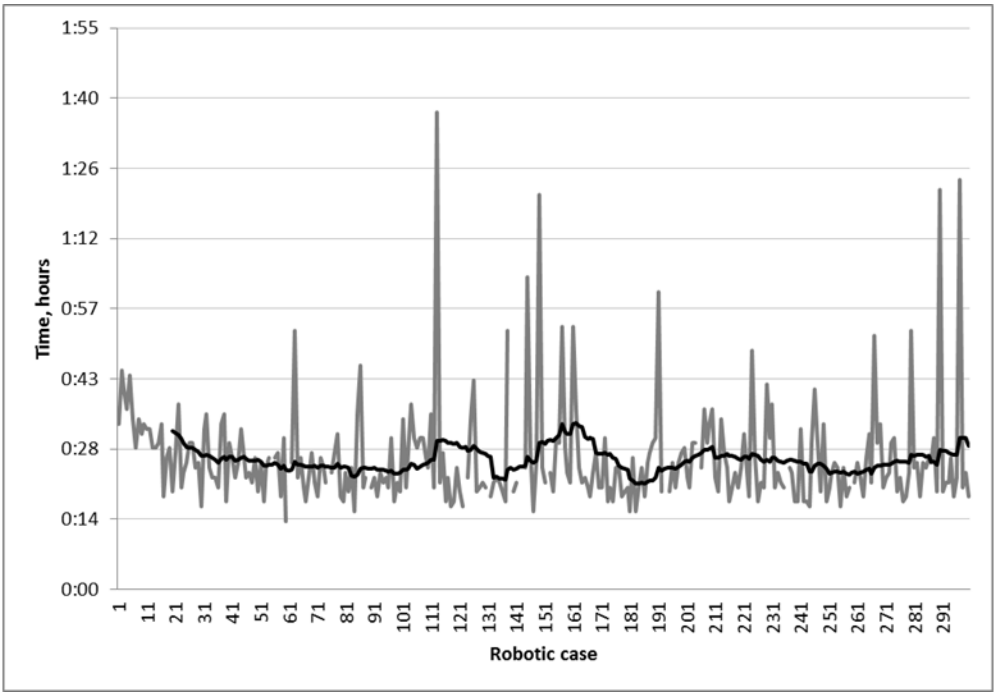


Figure 8. Set-up time, with moving average of 20 patients.

For the all 300 operations, the median docking time was 7 minutes (range 1–35). The docking time shortened significantly (*p*=0.003) between the first and last 50 operations [9 minutes (range 3–25) vs. 6 minutes (range 1–16), respectively] (Figure 9).

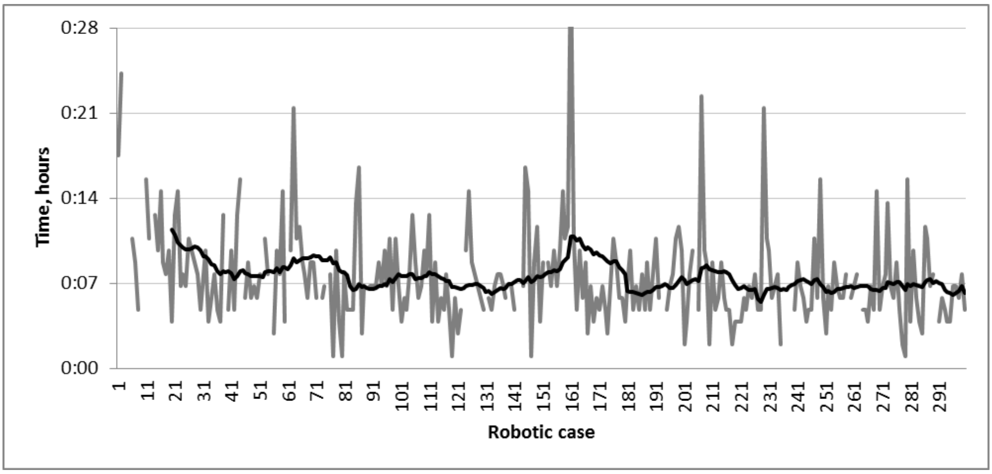


Figure 9. Docking time, with moving average of 20 patients.

The OR preparation time and docking time were measured for all 300 patients, regardless of the type of the operation. However, the learning curve for the operation time could only be assessed when all the operations were of the same type. Initially, all robot-assisted operations were performed on patients with endometrial carcinoma and all operations were the same: LH+BSO+PLND. These operations were the most common ones (n=89), and the median operation time was 167 (range 104-403) min. The first operation took 6 hours 43 minutes and the last 1 hour 44 minutes to perform. Median operation time was 260 (range 135-403) in the first 20 operations and 153 (range 104-247) min in the last 20 operations ($p<0.001$). The learning curve was evident in the operation time of this type of operations (Figure 10). After ten operations, there was no more clear decrease in the operation time. Also, the learning curves for surgeon A and surgeon B were very similar. For surgeon A, the median operation time for the first 10 and the last 10 operations was 243 (range 135–403) min and 132 (range 104–198) min, respectively ($p<0.001$) when for surgeon B it was 243 (range 179–294) min and 174 (range 120–197) min, respectively ($p<0.001$).

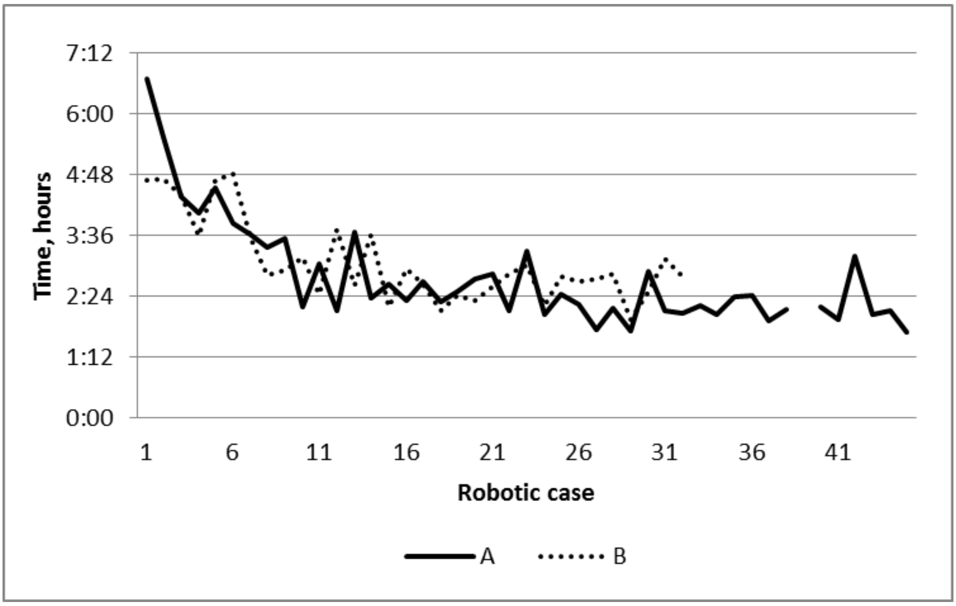


Figure 10. Hysterectomy, bilateral salpingo-ophorectomy and pelvic lymphadenectomy: Skin to skin operation time median was 167 minutes (range 104–403). A = surgeon A, B = surgeon B.

Taking into account all operations, console time had the biggest impact on the OR time (Figure 11).

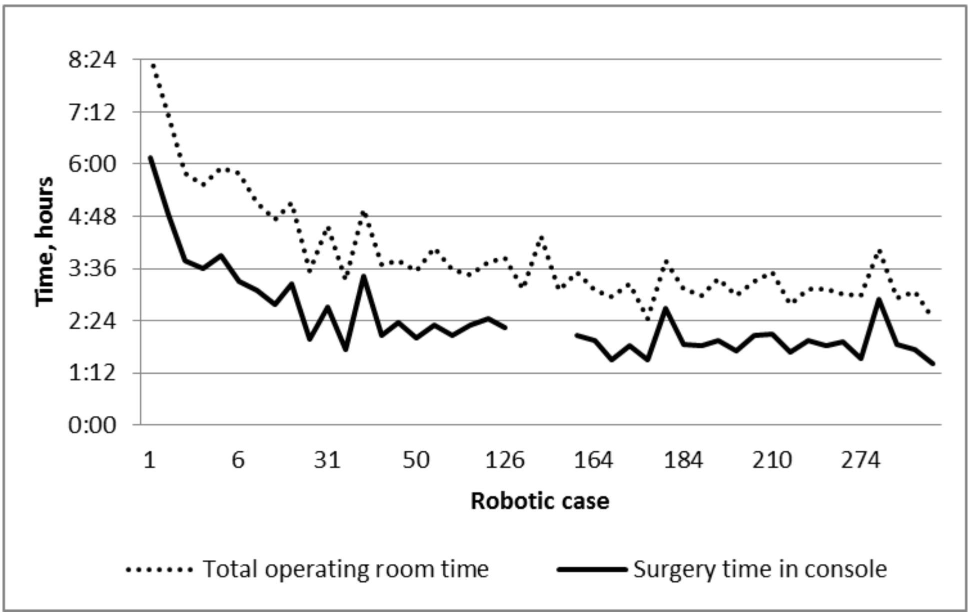


Figure 11. The console time is a determining factor in the use of the operating room.

4.1.2 Surgical outcomes

In the entire cohort, the median amount of intraoperative EBL was 100 ml (range 5–3200 ml), and the median hospital stay was 1 day (range 1–10). In cases where the operation had to be converted to open surgery 4% (12/300), the median hospital stay was 6 days (range 3–31).

4.1.2.1 Lymphadenectomy

Besides shortening of the OR time, training also had an impact on the surgical results. The number of lymph nodes removed in lymphadenectomy increased as the number of the procedures increased. Surgeon A performed the most endometrial cancer operations (LH+BSO+PLND), and in his operations the number of removed lymph nodes increased significantly between the first and the last operations (Figure 12). In the case of the first 20 operations, the median number of lymph nodes was 16 (range 5–33), and in the case of the last 20 it was 28 (range 13–44), respectively ($p<0.001$).

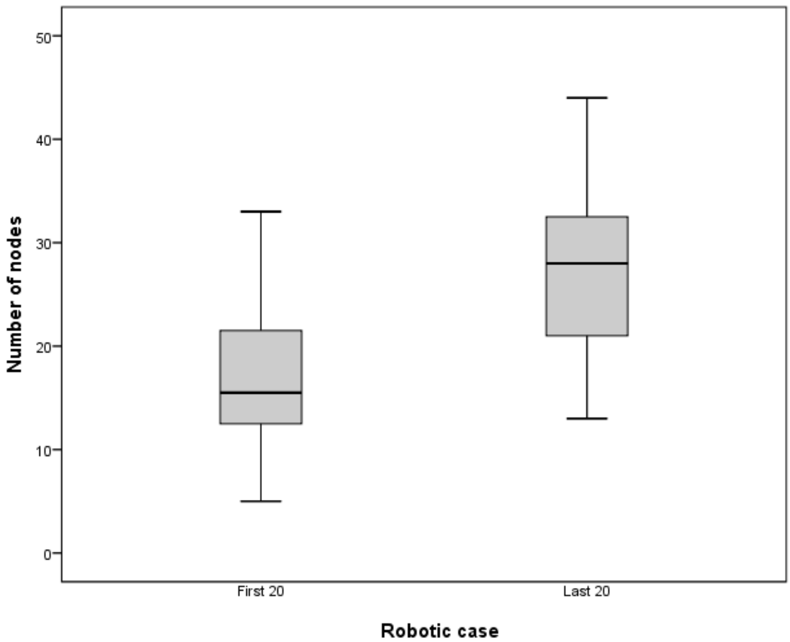


Figure 12. The number of pelvic lymph nodes surgeon A removed during his first and last 20 endometrial cancer operations (LH+BSO+PLND).

In the study I population (n=300), a lymphadenectomy was performed on 217 patients. Out of these, 213 had a PLND and 98 patients had a PALND. The median number of removed pelvic lymph nodes was 22 (range 0–57), and the median number removed para-aortic lymph nodes was 11 (range 0–38). The number of lymph nodes varied slightly in different types of operations. When the indication was cervical cancer, the median number of removed pelvic lymph nodes was 27 (range 13–57) and the median number of removed para-aortic lymph nodes was 20 (range 5–51). In the performed lymphadenectomies (n=217), lymph node metastasis was found in 10.6% of patients (23 patients with either cervical, ovarian, or high risk endometrial carcinoma).

4.1.2.2 Conversions and complications

Conversions had to be performed in 4% of the cases (12 out of 300 patients). However, in the primary operations for endometrial cancer (LH+BSO+PLND±PALND), the conversion rate was 2.2%. A major reoperation was performed on 5 out of 300 patients (1.7%), and the rate of vaginal vault dehiscence was 1.4% (3 hysterectomy patients). (Original Communication I, Table 2).

Complications were seen in 58 patients (19.3%), 27 of whom (9%) had major complications. Most of the complications (87%) were postoperative. The major type of complication was infection, half of which needed intravenous antibiotics (Original Communication I, Table 3).

4.2 Study II: Robotic-assisted versus traditional laparoscopic surgery for endometrial cancer

4.2.1 Operation time and OR time

Robot-assisted laparoscopy was significantly (18%) faster to perform than traditional laparoscopy on patients with endometrial carcinoma. The median operation time in the robotic group (n=50) was 139 (range 86–197) min, while it was 170 (range 126-259) min in the traditional laparoscopic group (n=49). The difference is statistically significant (p<0.001) (Figure 13).

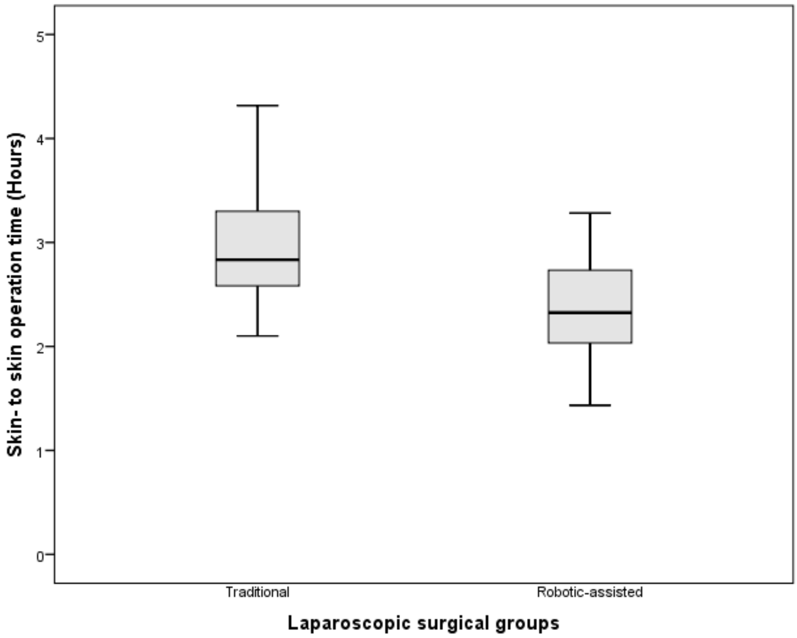


Figure 13. The median operation times in the traditional and robotic-assisted laparoscopic groups

While there were no conversions in the robotic group, five conversions had to be made in the traditional laparoscopy group. However, the operation time difference in favor of robotic-assisted surgery remained significant even when conversions were excluded. With the conversions excluded, the median operation time for traditional laparoscopy in the remaining patients (n=44) was almost the same as above or 171 (range 126–250) min, n=44 ($p<0.001$ vs. the robotic group).

In addition to operation time, also the OR time was shorter in the robotic-assisted surgery group. The median OR times of the robotic group and traditional groups were 197 (range 147–262) min and 228 (range 171–336) min, respectively. The difference is statistically significant ($p<0.001$).

4.2.2 Surgical outcomes

Between the robotic and traditional groups, there was no difference in the number of pelvic lymph nodes harvested, $p=0.273$. In the robotic group and the traditional group, the median number of pelvic lymph nodes removed was 25 (range 14–52) and 23 (range 11–50), respectively.

There were no significant differences in the surgical outcomes between the groups. Between the robotic and traditional groups, there was no significant difference e.g. in intraoperative EBL [Md. 50 ml (range 5–500) vs. 50 ml (range 20–1200), p=0.504] or length of the post-operative hospital stay [Md. one day (range 1–4) and two days (range 1–7), p=0.215], respectively. (Original Communication II, Tables 3 and 4).

Neither were there significant differences in complication rates, although the pattern of the complications was different between the study arms. 36% of patients had complications in the robotic group and 24% in the traditional group (p=0.275) (Original Communication II, Table 5). There were no intraoperative complications in the robotic group, but four patients had intraoperative complications in the traditional group (0% vs. 8%, p=0.056). There tended to be more postoperative complications in the robotic group than the traditional group (36% vs. 20%, p=0.085). Out of these patients, 22% and 10% had major complications, respectively (p=0.111). In this study, only one patient required a reoperation, in the robotic group (2%).

4.2.3 Effect of BMI and age

Obesity significantly increased the operation time in both groups. In patients with BMI>30 (n=48) and BMI<30 (n=51), the median operation time was 168 (range 104–259) min and 144 (range 86–227) (p=0.001), respectively (Table 13).

. Obese women had significant differences in the number of pelvic lymph nodes, amount of bleeding and length of the post-operative hospital stay compared to normal-weight women (Table 13 and Table 14). In patients with BMI>30 and BMI<30, the median number of pelvic lymph nodes was 27.5 (range 11–51) and 21 (range 13–47), respectively (p=0.001). Furthermore, in women with BMI>30 and BMI<30, the median amount of bleeding was 100 (20–1200) and 50 (5–400) ml (p=0.017).

The age on the other hand was not a significant factor in the operation time. Neither were there any significant age-related differences in surgical outcomes or postoperative events (Table 13 and Table 14).

Table 13. Operation times and surgical outcomes of the traditional and robotic study arms according to BMI and age:

	Traditional (N=49)		Robot (N=50)		p
ALL	**n=49**		**n=50**		
Operation time h:min, Md (Range)	2:50	(2:06-4:19)	2:19	(1:26-3:17)	<0.001
Bleeding ml, Md (IQR, Range)	50	(50-125; 20-1200)	50	(50-113; 5-500)	0.504
Conversions, n (%)	5	(10)	0	(0)	0.027
Intraoperative complications, n (%)	4	(8)	0	(0)	0.056
BMI<30	**n=26**		**n=25**		
Operation time h:min, Md (Range)	2:48	(2:06-3:48)	2:07	(1:26-2:50)	<0.001
Bleeding ml, Md (IQR, Range)	50	(50-100; 20-400)	50	(30-88; 5-300)	0.211
Conversions, n (%)	1	(4)	0	(0)	1.000
Intraoperative complications, n (%)	1	(4)	0	(0)	1.000
BMI≥30	**n=23**		**n=25**		
Operation time h:min, Md (Range)	3:03	(2:13-4:19)	2:33	(1:44-3:17)	0.001
Bleeding ml, Md (IQR, Range)	80	(50-200; 20-1200)	100	(50-175; 20-500)	0.891
Conversions, n (%)	4	(17)	0	(0)	0.046
Intraoperative complications, n (%)	3	(13)	0	(0)	0.102
Age<65	**n=17**		**n=19**		
Operation time h:min, Md (Range)	2:48	(2:12-4.10)	2:30	(1:26-3:13)	0.021
Bleeding ml, Md (IQR, Range)	80	(50-150; 20-700)	50	(50-150; 5-500)	0.452
Conversions, n (%)	2	(12)	0	(0)	0.216
Intraoperative complications, n (%)	1	(6)	0	(0)	0.472
Age≥65	**n=32**		**n=31**		
Operation time h:min, Md (Range)	2:52	(2:06-4:19)	2:12	(1:41-3:17)	<0.001
Bleeding ml, Md (IQR, Range)	50	(50-138; 20-1200)	75	(50-100; 10-400)	0.762
Conversions, n (%)	3	(9)	0	(0)	0.238
Intraoperative complications, n (%)	3	(9)	0	(0)	0.238

Table 14. Postoperative events in the traditional and robotic study arms according to BMI and age:

	Traditional (N=49)		Robot (N=50)		p
ALL	**n=49**		**n=50**		
Hospital stay, Md (IQR; Range)	2	(1-2; 1-7)	1	(1-2; 1-4)	0.215
Major early and late postoperative complications, n (%)	5	(10)	11	(22)	0.111
All complications total*, n (%)	12	(24)	18	(36)	0.275
Lymph nodes, Md (Range)	23	(11-50)	25	(14-51)	0.273
BMI<30	**n=26**		**n=25**		
Hospital stay, Md (IQR; Range)	1.5	(1-2; 1-5)	1	(1-2; 1-2)	0.520
Major early and late postoperative complications, n (%)	2	(8)	3	(12)	0.668
All complications total*, n (%)	5	(15)	7	(28)	0.460
Lymph nodes, Md (Range)	21	(13-47)	21.5	(14-41)	0.377
BMI≥30	**n=23**		**n=25**		
Hospital stay, Md (IQR; Range)	2	(1-3; 1-7)	1	(1-2; 1-4)	0.261
Major early and late postoperative complications, n (%)	3	(13)	8	(36)	0.173
All complications total*, n (%)	7	(30)	11	(44)	0.383
Lymph nodes, Md (Range)	24.5	(11-50)	29.5	(14-51)	0.266
Age<65	**n=17**		**n=19**		
Hospital stay, Md (IQR; Range)	1	(1-2; 1-3)	1	(1-2; 1-2)	0.471
Major early and late postoperative complications, n (%)	0	(0)	5	(26)	0.047
All complications total*, n (%)	3	(18)	7	(37)	0.274
Lymph nodes, Md (Range)	21	(15-40)	28	(14-51)	0.062
Age≥65	**n=32**		**n=31**		
Hospital stay, Md (IQR; Range)	2	(1-3; 1-7)	2	(1-2; 1-4)	0.344
Major early and late postoperative complications, n (%)	5	(16)	6	(19)	0.750
All complications total*, n (%)	9	(31)	11	(35)	0.595
Lymph nodes, Md (Range)	23.5	(11-50)	24	(14-44)	0.740

Md=Median; IQR=Interquartile range. Analyses were performed by Mann-Whitney test, Pearson chi-square test or by Fisher's exact test.

*All complications total was included intra operative, major and minor early postoperative, major and minor late postoperative complications. One patient may have >1 complication.

4.3 Study III: Costs of robotic-assisted versus traditional laparoscopy in endometrial cancer

4.3.1 Distribution of costs

As expected, robot-assisted laparoscopy was found to be more expensive than traditional laparoscopy in the treatment of endometrial cancer patients. The difference between these study groups was 35%. This difference is mostly due to the robot itself and its instrumentation.

The median cost for one operation was EUR 5,487 in traditional laparoscopy and EUR 7,415 in robotic-assisted laparoscopy, $p<0.001$. The robotic-assisted operation was thus EUR 1,928 more expensive (Original Communication III, Table 2).

In the robotic-assisted operation, the costs were more expensive than in traditional laparoscopy for instruments (Md. 1813 vs. EUR 214, $p<0.001$) equipment and OR (Md. 1172 vs. EUR 232, $p<0.001$) and post-anesthesia care unit time (Md. 938 vs. EUR 704, $p<0.001$) per operation (Figure 14). However, the costs were lower than in the traditional group for: Surgeon (Md. 735 vs. EUR 896, $p<0.001$), operation personnel (nurses and anesthesiologist) (Md. 729 vs. EUR 844, $p<0.001$), medication used (Md. 79 vs. EUR 91, $p<0.001$) and general costs (Md. 67 vs. EUR 78, $p<0.001$). Both groups had similar and marginal costs with regard to radiology services (Md. 0 vs. EUR 0, $p=0.321$) and blood products (Md. 18 vs. EUR 18, $p=0.674$). See Original Communication III, Table 2.

The amortization of the laparoscopy towers and the energy instrument (Sonosurg®) in the traditional laparoscopy group were included in the instrument costs. For most of the patients bi- and monopolar instruments were used, but the energy instrument was used in 15 operations. In each robotic-assisted surgery, 4 instruments were used (bipolar forceps, monopolar scissors, grasping forceps and one needle driver), and their cost per operation was EUR 1,030. The amortization cost of the robot console per operation was EUR 939 (equipment and OR costs). The amortization cost was included in the OR costs, and the OR costs were calculated based on the operation time (EUR 5.95/min). The operation time and the OR time were significantly shorter, but PACU time was significantly longer in the robotic group.

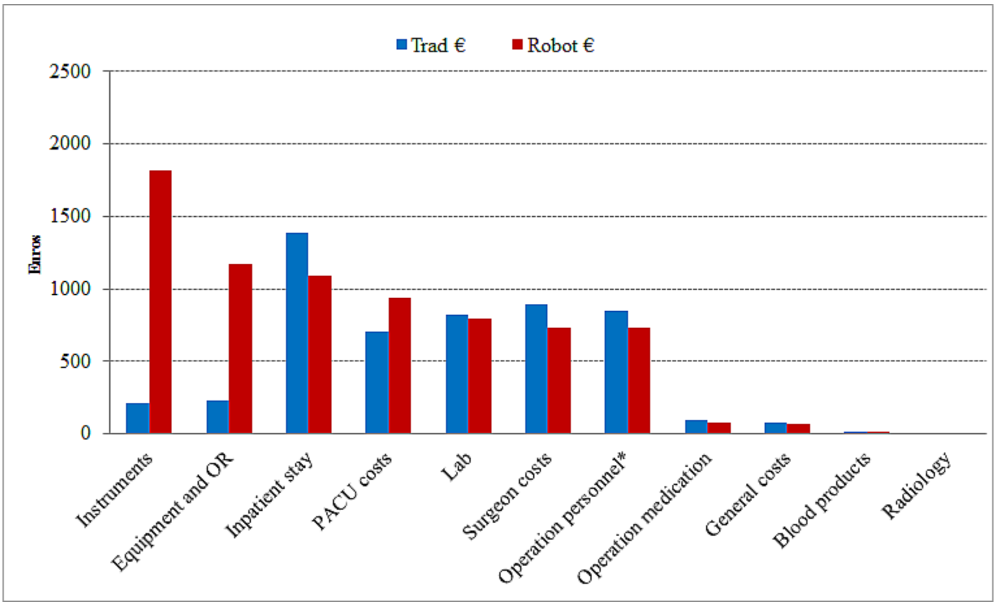


Figure 14. Total costs of the operations in the study arms

4.3.2 The cost impact of conversions and complications

In the study population there were 5 conversions into open surgery in the traditional group but no conversions in the robotic group. This narrowed the cost difference between the groups, because the cost of traditional laparoscopy converted into open surgery is almost as high as of robotic-assisted surgery (Md. traditional laparoscopy converted to open operation EUR 7,149 and robotic-assisted laparoscopy EUR 7,415). On the other hand, the total costs without conversions and without late complications in the traditional laparoscopy patients were significantly less than in traditional laparoscopic operations which ended up in conversion. (Md. non-conversions EUR 5,352 vs. conversions EUR 7,149, p<0.001). In traditional laparoscopy operations (non-conversions vs. conversions), the cost difference was due to the length of inpatient stay (Md 1 vs. 4 days, p <0.001) and PACU time (Md. 2h22min vs. 3h33min, p<0.001). Conversions vs. non-conversions increased the costs of the inpatient stay (EUR 2,148 vs. EUR 1,114, p=0.002) and the PACU costs (EUR 938 vs. EUR 704 p<0.001).

In addition to intraoperative and inpatient complications, complications in both groups were reviewed for the 6-month period following the surgery. 20 patients sought treatment in the robotic group and 10 patients in the traditional group.

During this time period, there was no significant difference in complication costs between the groups (robotic 844 (range 421–2,883) vs. traditional EUR 766 (range 349–1,532), $p=0.530$). The median total costs including late complications were EUR 7,982 in robotic-assisted surgery (range 7,236–8,400) and EUR 5,823 in traditional laparoscopy (range EUR 4,912–6,243) ($p<0.001$). The total costs of robotic-assisted laparoscopy, with complications, was EUR 2,160 higher (1.4-fold) than traditional laparoscopy.

4.4 Study IV: Robotic-assisted infrarenal para-aortic lymphadenectomy in gynecological cancers

4.4.1 PALND level

PALND succeeded above the IMA level in 83% (235/283) of PALND procedures (Figure 15). Out of these, the most cranial level (the level of the renal vein or at least four cm above the IMA) was reached in 69 operations. The height reached above the IMA was three cm in 79 operations, two cm in 36 operations and one cm in 29 operations. In addition, the highest level, between the IMA and the renal vein, was reached in 22 PALND procedures but the surgeon did not specify the level of dissection. In 19 patients (7%), PALND procedure was performed up to the IMA level, and in 8 procedures (3%), the level stayed below the IMA. In 17 patients (6%), PALND procedure was incomplete, and only a para-aortic lymph node biopsy was taken from these patients. PALND was performed for four additional patients (1%) but the extent of the procedure or the level was not specified.

Obesity was the major reason for failure to remove lymph nodes from a high level. PALND remained significantly more often at the IMA level or below when the patient's BMI was ≥ 33 as compared to patients with BMI < 33 ($p<0.001$). In over half of the patients (56%) with incomplete PALND, BMI was ≥ 33, when in the entire material only 27% of the patients had BMI ≥33.

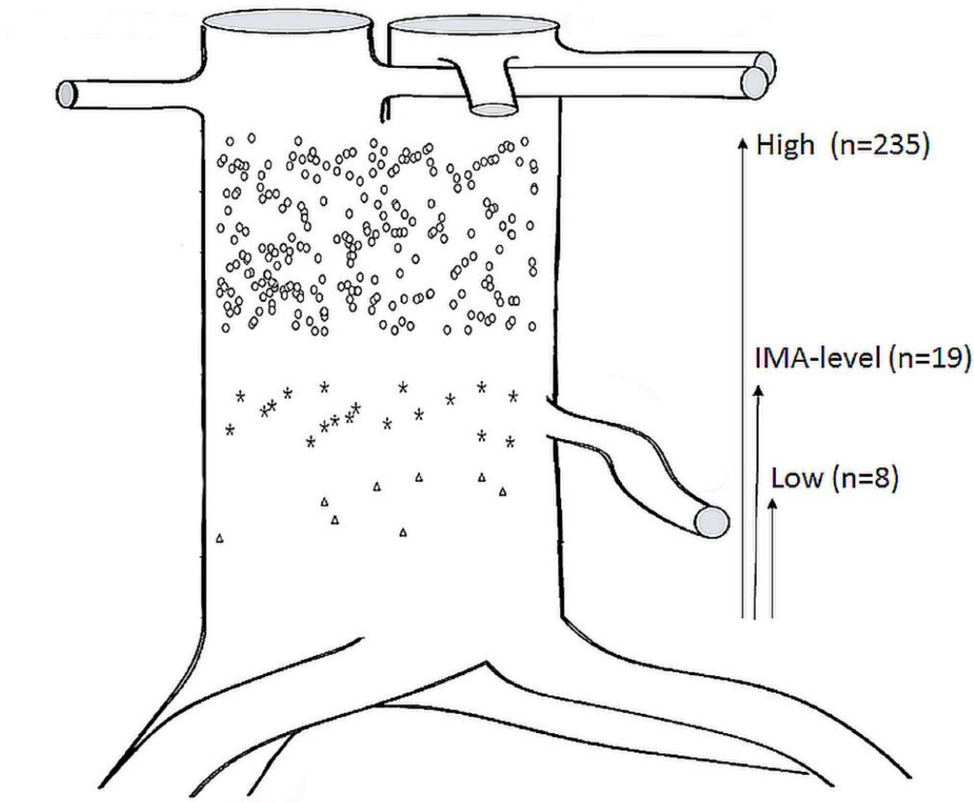


Figure 15. In PALND, the direction is from down to up, and the marks show the level up to which the surgeon performed the procedure.

4.4.2 Lymph nodes and metastases

The number of removed para-aortic lymph nodes did not correlate with patient BMI (rho = 0.077, *p*=0.196). It did, however, positively correlate with longer patient height to some extent (rho=0.128, *p*=0.032). Moreover, a short stature (≤ 162 cm) of the patient and the presence of intra-abdominal adhesions tended to have a negative effect on the success rate of the high PALND (*p*=0.091 and *p*=0.085, respectively).

The median number of harvested para-aortic lymph nodes was 12 (range 0–38), and 23 (range 0–88) for pelvic nodes (Table 15). Out of all patients, 6 (2.1%) did not have lymph nodes in the final histopathology results. Table 15 also specifies the number of lymph node metastases.

Table 15. The number of the lymph nodes and the number of lymph node metastases (283 operations).

	Patients	Number of lymph nodes		Total number lymph nodes removed	Total number of lymph node metastases	
Lymphadenectomy area	N	Md	(Range)	N	n	(%)
Para-aortic lymph node count	283	12	(0-38)	3636	136	(3.7)
Pelvic lymph node count	276	23	(0-88)	6846	137	(2.0)
Iliac area	274	10	(0-56)	2988	71	(2.4)
Obturator area	275	13	(0-40)	3853	61	(1.6)

In the whole PALND cohort (283), metastatic lymph nodes were found in 61 patients (22%): 18 patients had metastases in pelvic lymph nodes, 20 patients in para-aortic lymph nodes and 23 patients in both. In other words, 30% had metastases only in the pelvis, 33% only in the para-aortic region and 38% both in the pelvic and para-aortic lymph nodes.

Most of the patients had high risk endometrial cancer and their lymph node metastases were reviewed separately. Of the patients with endometrial cancer, 175 had the endometrioid type endometrial carcinoma, out of whom 38 had lymph node metastases (also 22%). In this group, the results did not significantly differ from the whole cohort with regard to the sites of metastases (*p*= 0.89): 11 (29%) had only pelvic metastases, another 11 (29%) had only para-aortic metastases, while 16 (42%) had both pelvic and para-aortic metastases.

4.4.3 Learning curves of PALND

The number of para-aortic lymph nodes removed per operation increased as the surgeon gained more experience. In the entire cohort, PALND procedures were performed by 5 surgeons, and the number of lymph nodes they removed per operation is presented in Figure 16. After approximately 40 operations, there was a change in the number of lymph nodes removed, with more nodes removed after than before 40 operations. Surgeons 1, 2 and 3 performed the greatest number of operations, and in their operations, the number of lymph nodes was significantly higher at the end of the learning curve than in the first operations. The median number of removed para-aortic lymph nodes was 11.5 (range 0–26) in the first ten operations and 18 (range 1–35) in the last ten operations (*p*=0.004).

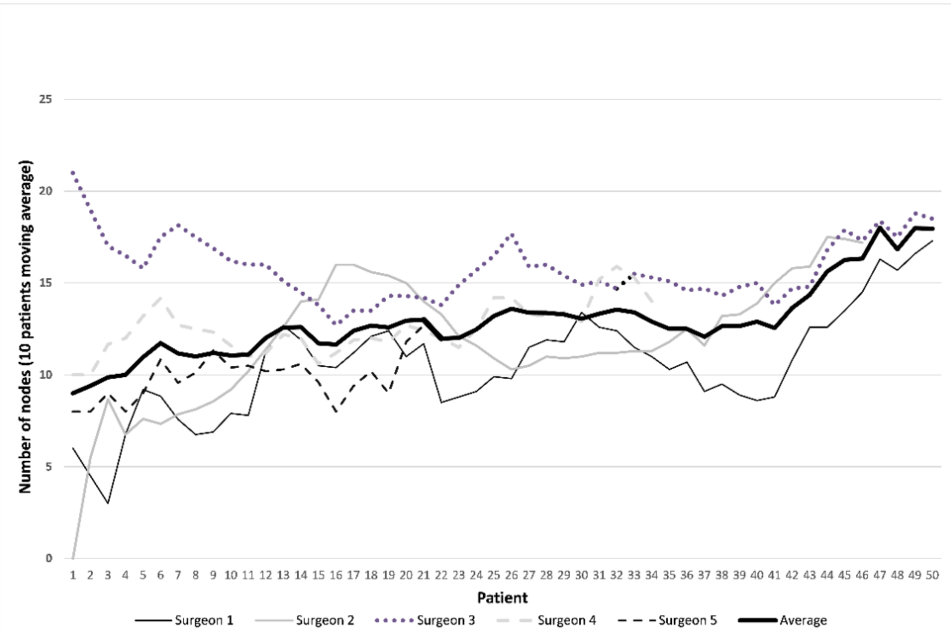


Figure 16. The learning curves for the five gynecologic surgeons performing the para-aortic lymph node dissections, in terms of the total number of lymph nodes harvested. Each thin line represents the curve for one surgeon, and the thick line describes the mean number of nodes harvested as a function of increasing number of operations performed

4.4.4 Surgical outcomes

The median EBL was 100 ml (range 10–1,400). Hysterectomy was performed on 82% of the patients, and the median uterine weight was 111 g (range 33–664). In 6.1% of the patients (14/231), the uterus was removed by a mini-laparotomy through a small (max. 10 cm) Pfannenstiel incision, due to a large uterus and/or narrow vagina. The median uterine weight of these patients was 298 g (range 140–664). In this mini-laparotomy group (n=14), the median length of the post-operative hospital stay was two days (range 1–3). In the entire material, the median length of the post-operative hospital stay was also two days (range 1–8) (n=273). Ten patients (7 conversions and 3 re-operations) underwent laparotomy, and their median length of post-operative hospital stay was 6.5 days (range 3–31, n=10).

In seven patients (2.5%), laparoscopy was converted to laparotomy (Original Communication IV, Table 1). Adhesions were the cause in five cases and disseminated cancer in two. No conversions were made in standard/primary operations (LH+BSO+PLND+PALND) performed due to endometrial cancer. The rate of re-operations was 3.5% (n=10), of which seven were major (laparotomy, n=3; a vaginal operation, n=4), while three were minor (all vaginal).

68 patients (24%) had complications, out of which 31 patients (11%) had major complications and 37 (13%) minor complications, respectively (Original Communication IV, Table 4). 3.5% of patients had intraoperative complications. Nearly half of the postoperative complications were infections, and 42% (13/31) of these were treated with intravenous antibiotics. A symptomless postoperative lymph cyst was found in twenty-six patients (9%). After discharge, 47 patients (17%) had to seek treatment for some symptom.

Most of the patients, 215 (76%), received some adjuvant therapy after surgery: Combination of chemotherapy and external radiation (n=80, 28%), chemotherapy (n=37, 13%), external radiation (n=11, 4%), brachytherapy (n=58, 21%), combination of chemotherapy and brachytherapy (n=28, 10%), and chemoradiation (n=1, 0.4%).

4.5 Summary of studies I, II and IV on robotic-assisted surgery for endometrial cancer

Table 16. Summary table

	Summary of studies on robotic-assisted surgery for endometrial cancer					
	Study I		**Study II**		**Study IV**	
	LH + BSO + PLND±PALND		LH + BSO + PLND		LH + BSO + PLND+PALND	
	n=134		n=50		n=160	
Statistics	Md	(range)	Md	(range)	Md	(range)
Age	68	(41-86)	67	(43-84)	69	(41-84)
BMI	30	(20-46)	29	(20-46)	29	(19-46)
Length of operation (min)	183	(104-403)	139	(86-197)	218	(140-341)
Preparation time*	42	(19-92)	45	(31-62)	41	(21-97)
Set-up time**	25	(16-53)	17	(10-38)	24	(11-104)
Docking time***	7	(1-25)	6	(1-16)	7	(1-37)
Pelvic nodes	20	(5-51)	25	(14-52)	24	(5-88)
PA nodes	10	(0-28)	n.d		12	(0-35)
Blood loss (mL)	100	(10-3000)	50	(5-500)	100	(10-500)
Hospital stay (day)	2	(1-10)	1	(1-4)	2	(1-6)
Conversion rate	2.2	%	0	%	0	%
Complication rate	19.4	%	36	%	27.5	%
Major complication	9	%	22	%	12.5	%
Intraoperative complication	2.2	%	0	%	4.4	%

* The time that elapsed from the arrival of the patients to the OR until the start of the operation

** The time that elapsed from the start of the operation until the start-up of the robotic console, including docking time

*** The time it took to attach the robot and the instruments on the patient

5 DISCUSSION

5.1 Implementing robotic-assisted surgery to gynecologic oncology

At the Department of Obstetrics and Gynecology of Tampere University Hospital, robotic-assisted laparoscopic surgery was started with operations for endometrial carcinoma. The limited resources for robotic-assisted operations (maximum two operations / week) were acknowledged from the beginning, and the operations were focused on demanding cancer operations. Despite this, the implementation and adoption of the robotic-assisted surgery took place with surprising ease, thanks to the well-trained and dedicated robotic team carefully following the instructions for robotic-assisted laparoscopic technique.

5.1.1 The learning curves

The learning curves were constructed based on standard procedures, which adds to the reliability of the study results. The preparation time shortened significantly with increasing experience (a median 22-minute difference between the first and last 50 between the last fifty patients than for operations in Study I), which is a novel finding.

The learning curve for the operation time took ten operations to become established in Study I, and was similar by the first two surgeons. The learning curve could not be evaluated for the surgeons that started performing robotic-assisted surgery later because their learning process was different. They started to perform operations gradually, e.g. performing initially only hysterectomy or PLND rather than the whole operation.

In other published studies the learning curve has been somewhat longer. Lowe et al. found that, in operations for endometrial carcinoma, the learning curve was 9–20 operations (Lowe, Johnson et al. 2009), whereas according to Seamon et al. it is 20 operations (Seamon, Fowler et al. 2009) and according to Lim et al. 24 operations (Lim, Kang et al. 2011). However, the study of Lim et al. included also PALND, which naturally is prone to make the training more difficult. The difference between the present and other studies may at least partly be explained by the long tradition for performing laparoscopic hysterectomies in Finland (Mäkinen, Johansson 2001, Kuoppala, Tomás et al. 2004). In the above-mentioned studies, the transition to robotic-assisted surgery has mainly taken place from laparotomy, and not from traditional laparoscopy (DeNardis, Holloway et al. 2008). In robotic-assisted laparoscopy, the learning curve has been found to be twice as fast in comparison to traditional laparoscopy (24 vs. 49) (Lim, Kang et al. 2011).

Console time was found to be the most important factor affecting OR time in the present study. Iranmanesh et al. indicated in their study that in addition to the actual console work, also pre-operation and docking times are significant areas of learning. Their finding was in line with ours: Learning curves are fast when attention is paid to the work of the entire OR team. They also found that the docking time of surgeons who performed over 10 operations was significantly shorter than that of inexperienced surgeons. The median docking time in the first five operations was 10-15 minutes, while it shortened to 3-4.5 minutes in the last five operations (Iranmanesh, Morel et al. 2010). In our study, median docking time was 6–7 minutes (studies I–IV).

In the learning curve studies, we assessed the combined operation and console time and their decrease. Unfortunately, we did not specify how different surgical stages were learned at the console. Seamon et al. analyzed the learning of the various console steps. Hysterectomy was the quickest to learn, approximately 20 operations, but the curve stabilized only after approximately 70 operations. Lymphadenectomies took longer to learn (Seamon, Fowler et al. 2009). Also in the study by Tang et al., this analysis was performed for operations where the uterus was removed due to benign reasons. They found that the learning curve was 8 operations for console work and 14 operations for the docking phase. Learning was slowest in suturing, where the learning curve was 26 operations (Tang, Tsai 2017). Lim et al. reported similar results for patients with endometrial carcinoma: learning of docking and trocar placement took 10 operations, hysterectomy 8 operations, vaginal cuff closure 21 operations, pelvic node dissection 55 operations and para-aortic node dissection 17 operations (Lim, Kang et al. 2011). Even if the time used for lymphadenectomy was not measured separately in Study I, also our results suggest that learning decreases the procedure time in lymphadenectomy. In LH+BSO+PLND operations, the median operation time was 260 and 153 min for the first and last 20 operations, respectively.

As well as time-wise improvement, learning in terms of the quality of robotic-assisted surgery took place during the follow-up period. As more procedures are performed, the surgical technique and tissue dissection improves, also leading to increasing number of removed lymph nodes. In LH+BSO+PLND operations (Study I), the median number of lymph nodes increased from 16 to 28 between the first and last 20 operations ($p<0.001$). The same finding was observed in study IV, where the median number of removed para-aortic lymph nodes increased from 11.5 to 18 between the first 10 and the last 10 operations ($p=0.004$). Holloway et al. similarly found that the number of lymph nodes increased between the first and the last 10 operations out of 100 (pelvic nodes from 15 to 21, and para-aortic nodes from 5 to 8) (Holloway, Ahmad et al. 2009). A similar trend has been observed earlier in traditional laparoscopy: the number of lymph nodes increased as the surgeon gained more experience, even after four years (Holub, Jabor et al. 2003).

The number of lymph nodes in PALND operations increased even after 40 operations (Study IV), referring to the more demanding nature of lymph node dissection in para-aortic area, as compared to PLND.

5.1.2 The operation times

Previous retrospective studies have repeatedly indicated that robotic-assisted surgery is more time-consuming than traditional laparoscopy (Corrado, Cutillo et al. 2015, Seror, Bats et al. 2014, Bell, Torgerson et al. 2008, Cardenas-Goicoechea, Adams et al. 2010). Thus, the hypothesis for the randomized trial (Study II) was that robotic-assisted surgery would take 25% longer time to perform than traditional laparoscopic surgery. However, robotic-assisted laparoscopy turned out to be significantly faster than traditional laparoscopy on patients with endometrial carcinoma (139 vs. 170 minutes; 18%).

In addition to shorter operation time, also the OR time was significantly shorter in the robotic group. This result was also surprising because, in advance, preparation time of the OR was expected to more time consuming when using robot technology. In the study by Leitao et al., the median OR time was 45 minutes longer in robotic-assisted operations than in traditional laparoscopic operations for endometrial cancer ($p<0.001$), and the median operation time was 29 minutes longer ($p<0.001$) (Leitao Jr, Briscoe et al. 2012).

In obese patients, abdominal surgery in general is challenging to perform. Consequently, complications like wound infections are more common (Amri, Bordeianou et al. 2014). Mini-invasive operations in obese women are associated with a shorter postoperative stay and a lower complication rate than laparotomies (Chan, Gardner et al. 2015). The operation time for obese women was longer than for normal-weighed women in both groups of Study II. In the traditional group, median operation time for patients with BMI ≥ 30 was 15 minutes longer, and in the robotic group, 26 minutes longer than for patients with BMI < 30. However, median operation time for patients with BMI ≥ 30 was 30 minutes shorter when using robotic-assisted technique than when using traditional laparoscopy. Robotic-assisted technique seems thus to be more suitable for overweight patients. Because women with endometrial carcinoma are often obese, they represent an important target group for robotic-assisted surgery (Eisenhauer, Wypych et al. 2007, Scribner, Walker et al. 2002, Chan, Gardner et al. 2015).

5.1.3 Lymph node dissection

The Study II did not reveal a significant difference between the number of removed lymph nodes between traditional and robotic-assisted laparoscopy, but the numbers were high in both groups, which indicates that the techniques were successful in both groups. The median number of pelvic lymph nodes was 25 in the robotic group and 23 in the traditional group. In previous non-randomized studies, the median (or mean) number of pelvic lymph nodes has varied between 12-25 in both robotic-assisted and traditional laparoscopic operations (Seamon, Cohn et al. 2009, Bell, Torgerson et al. 2008, Cardenas-Goicoechea, Adams et al. 2010, Coronado, Herraiz et al. 2012, Leitao, Briscoe et al. 2012). The only studies, where the difference has been significant in favor of the robotic-assisted operations, are the ones by Boggess (21 vs. 17) and Gehrig et al. (22 vs.18) (Boggess 2008, Gehrig, Cantrell et al. 2008). However, in the study by Lim et al., a larger number of lymph nodes was harvested in traditional laparoscopy than in robotic-assisted laparoscopy (25 vs. 19, respectively) (Lim, Kang et al. 2011).

In all Studies I–II and IV, the median number of pelvic lymph nodes was in the range of 22–27 and that of para-aortic lymph nodes 11–12. The numbers of removed lymph nodes are higher than in several other studies (Veljovich 2008, Bell, Torgerson et al. 2008, DeNardis, Holloway et al. 2008, Boggess 2008, Lowe, Johnson et al. 2009, Seamon, Fowler et al. 2009, Hoekstra, Jairam-Thodla et al. 2009, Cardenas-Goicoechea, Adams et al. 2010). In a multi-institutional study Lowe et al. in 2009 analyzed 405 robotic-assisted endometrial cancer operations, and the median number of pelvic lymph nodes was 12 while the median number of para-aortic lymph nodes was only 2 (Lowe, Johnson et al. 2009). Similarly, a study by Leitao et al. in 2012 found that the median number of pelvic lymph nodes was 13, whereas the median number of para-aortic lymph nodes was 6 (Leitao Jr, Briscoe et al. 2012). We do not have follow-up data yet, but previous studies imply that the patients who have at least 10 nodes removed and from many areas have a survival benefit and a better chance to have lymph node metastases detected (Lutman, Havrilesky et al. 2006, Chan, Cheung et al. 2006, Chan, Urban et al. 2007, Cragun, Havrilesky et al. 2005, Mahdi, Kumar et al. 2013, Huang, Chadha et al. 2010).

In Study IV the median number of removed para-aortic lymph nodes was 12. This compares well with those studies that used the same technique, where the median number of removed para-aortic lymph nodes has been in the order of 6–15 (James, Rakowski et al. 2015, Geppert, Persson et al. 2015, Franké, Narducci et al. 2015).

In addition to a sufficient number of lymph nodes, a good para-aortic lymphadenectomy technique includes removing nodes from a sufficiently extensive area. In gynecological patients, this means removing lymph nodes up to the renal veins. In Study IV, a high level of PALND succeeded above IMA in 83% of operations and up to renal vessels in 24% of the patients. If performed, PALND is either the first step in every operation or second only to the removal of the omentum. The dissection is started from the right side, moving from above the pelvis towards the upper abdomen and then downward on the left side of the aorta. (Abu-Rustum, Sonoda 2007).

Other studies that have used the same technique as we (transperitoneal approach, SD between the legs, a deep Trendelenburg position and a high placement of trocars in the upper abdomen) have also reported good results. James et al. succeeded in reaching the high infrarenal level in 90.7% of PALND procedures, and Geppert and Persson reported a success rate of 70%. The success rate increased to 79%, if the results of more inexperienced surgeons were excluded. It thus seems that experience helps a surgeon to achieve good PALND results (Lambaudie, Narducci et al. 2012, Pakish, Soliman et al. 2014, James, Rakowski et al. 2015, Geppert, Persson et al. 2015). This is also indicated by the present PALND learning curve result, according to which the number of lymph nodes increased clearly even after 40 operations.

One measure of high-quality lymphadenectomy is the number of discovered metastases. In Study I, lymph node metastases were found in 10.6% of patients. It should be noted that lymph node metastases were not found in any patients with low-risk endometrial carcinoma. In Study II, lymph node metastases were found in two patients in the robotic-assisted surgery group (4%). These results support the current recommendation not to perform lymphadenectomies for low-risk endometrial carcinoma (Dowdy, Borah et al. 2012, Morice, Leary et al. 2016, Colombo, Creutzberg et al. 2016).

The population of Study IV consisted of high-risk patients (high risk endometrial, cervical and ovarian cancer) and consequently, the incidence of lymph node metastasis was high. The proportion of patients with lymph node metastases was 22% (61/283) in the whole study population with a mixture of gynecological malignant tumors, which is considerably higher than the proportion (6%) was in the review of 898 patients by Iavazzo and Gkegkes (Iavazzo, Gkegkes 2016).

In the 175 patients with endometrioid endometrial carcinoma in Study IV, the rate of lymph node metastasis was again 22%. Especially the rate of para-aortic lymph node metastases was surprisingly high (15%) in these patients, and 11 (6%) of them had only para-aortic metastases. These findings indicate that we had succeeded in the selection of high-risk patients for the operations (deep invasion, grade 3 or HGSC). In earlier studies, the rate of para-aortic metastases, and especially of the metastases only in the para-aortic area, has been lower: 3% and 1% or 12% and 3%, respectively (Dogan, Gungor et al. 2012, Kumar, Podratz et al. 2013). A successful para-aortic lymphadenectomy is very important in the planning of adjuvant therapy for high-risk patients. 76% of the high-risk patients with endometrial carcinoma (Study IV) received some form of adjuvant therapy.

The fact that patients with high-risk endometrial carcinoma were discovered to have so many lymph node metastases in the para-aortic area support current clinical guidelines recommending both PLND and PALND (Colombo, Creutzberg et al. 2016).

5.1.4 Safety of robotic-assisted laparoscopic surgery

In laparoscopic operations, a low number of conversions is a good measure of quality. The conversion rate of the robotic-assisted operations was 4.3%, 0% and 2.5% in Studies I, II and IV, respectively. The number of conversions in operations for endometrial cancer has varied in previous studies between 0.5% - 12% (Seamon, Cohn et al. 2009, Lowe, Johnson et al. 2009, Paley, Veljovich et al. 2011, Cardenas-Goicoechea, Soto et al. 2012).

In the randomized Study II, all of the five conversions [due to adhesions (2), disseminated cancer (1), bleeding from the abdominal wall (1), or a uterus too large to be removed through the vagina (1)] had to be made in traditional laparoscopy group, which is in line with the previous literature. In their 2010 study, Cardenas-Goicoechea et al. detected very few conversions in both 102 robotic-assisted operations and 173 conventional laparoscopy of endometrial cancer patients. There was only one conversion in the robotic group and nine in the laparoscopy group. Also in the case-control study of Lim et al. on 244 staging operations, the conversion rate was only 0.8% in robotic-assisted operations, while it was 6.5% in the traditional laparoscopy group, p=0.036 (Cardenas-Goicoechea, Adams et al. 2010).

In Study IV the conversions concentrated in the secondary staging operations and in operations involving complex procedures. There were no conversions in standard LH+BSO+PLND+PALND operations for endometrial carcinoma. In previous studies using the same PALND operating technique as described above, the conversion rate has varied between 0 – 5% (Pakish, Soliman et al. 2014, James, Rakowski et al. 2015, Geppert, Persson et al. 2015).

In addition to conversions, re-operations decrease the quality of operations and increase the risk of prolonged recovery and decreased quality of life. In Studies I, II and IV the rate of re-operations was 2.7% (8/300), 2% (1/50) and 3.5% (10/283), respectively. Seven complications required laparotomy, and two could be treated with laparoscopy. Half of the re-operations were performed due to a postoperative vaginal vault dehiscence, and could be repaired vaginally. Our results are in line with previous studies. According to the study and literature review by Uccella et al., the incidence of vaginal cuff dehiscence following robotic-assisted hysterectomy is 1.64% and 0.66% in conventional laparoscopy (Uccella, Ghezzi et al. 2011) In robotic-assisted operations, the rate of vaginal cuff dehiscence has varied between 0–4% following hysterectomy (Cronin, Sung et al. 2012, Drudi, Press et al. 2013), and approximately 6% following radical robotic-assisted hysterectomy (Persson, Reynisson et al. 2009, Drudi, Press et al. 2013).

The use of bidirectional barbed sutures has been found to prevent vaginal cuff dehiscence. Siedhoff et al. reported zero versus 4.2% rate of dehiscence (p= 0.008) in 387 patients using barbed sutures vs. conventional closure, respectively (Siedhoff, Yunker et al. 2011). This new technique deserves to be explored in practice.

The risk of intraoperative bleeding increases in demanding operations. In surgery for gynecological cancer, tissue and lymph nodes are removed from areas surrounding large vessels (e.g. vena cava, aorta, IMA, and iliac arteries and veins), carrying always a risk for major bleeding. However, bleeding was found to be quite minimal in robotic-assisted laparoscopy. The median EBL was 100, 50 and 100 ml in Studies I, II and IV, respectively. In previous studies on endometrial cancer, EBL has been in the same range; in 13 out of 16 studies listed in Table 8, the EBL was 50-100 ml.

The complication rate of the robotic-assisted laparoscopy in Studies I, II and IV is shown in Table 17, along with data from 14 previous studies. Early postoperative complications took place before discharge and late complications following discharge but during the next six months. For the complications, the degree of difficulty/severity was estimated. Major complications included a re-operation, bowel, bladder or ureteric injury, cardio-pulmonary event (infarction, atrial fibrillation, respiratory insufficiency, embolism or thrombus) vascular injury and major bleeding (a decrease in the HgB level exceeding 40 g/L, or need for transfusion or estimated blood loss exceeding 500 mL), infection requiring intravenous antibiotics, symptomatic lymph cyst, permanent damage (nerve injury, hernia, fistula, miscarriage). Minor complications included wound or port-site bleeding, vaginal cuff hematoma or defective healing, urine retention, wound or urinary tract infection requiring oral antibiotics, symptomless lymph cyst, minor foot swelling.

Our intraoperative complication rate 0-3.5% comparable with other studies, where it has varied between 0-6.2%. Also, the postoperative complication rate in Studies I and IV is very similar to other studies. An outlier is the randomized Study II, where the postoperative complication rate was 36% or bigger than in any other study cited. The difference is difficult to explain, because it cannot be caused by a more meticulous follow-up only, as the postoperative complication rate was only 20% in the traditional laparoscopy group. Most other studies have not given data on complications as divided to major and minor, but as compared to Paley et al. and Lim et al., our rates seem to be somewhat higher. However, the cross-trial comparisons are difficult to make reliably, as the definitions of complications and the way they are presented, differ between the studies.

The study IV complication rate of the para-aortic lymphadenectomy patients is consistent with previous PALND literature, where it has been reported to be 14% - 36%. The same holds true for the reported rate of major complications: 8% - 14% (Ekdahl, Salehi et al. 2016, Hudry, Ahmad et al. 2015, Geppert, Persson et al. 2015, James, Rakowski et al. 2015).

In the present study, the complications were treatable and no fatality related to the operations occurred. No operative mortality was reported in the studies by e.g. Lim et al., Bandera et al. or Cardenas-Goicoecchea, eithers (Lim, Kang et al. 2011, Cardenas-Goicoechea, Shepherd et al. 2013).

Table 17. Summary of complications related to robotic-assisted laparoscopy in different studies

		Complications in robotic-assisted laparoscopy				
		Intra-operative complications	Post-operative complications	Patients with complications		
				Total	Major	Minor
Study	N	n (%)	n (%)	n (%)	n (%)	n (%)
Study I*	300	9 (3%)	61 (20%)	58 (19%)	27 (9%)	31 (10%)
Study II*	50	0 (0%)	18 (36%)	18 (36%)	11 (22%)	7 (14%)
Study IV*	283	10 (3.5%)	64 (23%)	68 (24%)	31 (11%)	37 (13%)
Comparison						
Wright 2012	1437	43 (3%)	n.d	115 (8%)	n.d	n.d
Paley 2011	1000	n.d	n.d	100 (10%)	57 (5.7%)	42 (4.2%)
Lowe 2009	405	14 (3.5%)	59 (15%)	73 (18%)	n.d	n.d
Leitao 2012	347	n.d	n.d	35 (10%)	n.d	n.d
Cardenas-Goicoechea 2013	187	3 (1.6%)	37 (20%)	n.d	n.d	n.d
Lim 2011	122	1 (0.8%)	n.d	13 (11%)	5 (4%)	7 (6%)
Seamon, Cohn 2009	105	n.d	n.d	11 (13%)	n.d	n.d
Boggess 2008	103	1 (1%)	5 (5%)	6 (6%)	n.d	n.d
Cardenas-Goicoechea 2010	102	2 (2%)	10 (10%)	27 (27%)	n.d	n.d
Chiou 2015	86	n.d	n.d	2 (2.3%)	n.d	n.d
Corrado 2015	72	1 (1.4%)	3 (4.2%)	n.d	4 (6%)	n.d
Coronado 2012	71	2 (3%)	13 (18%)	15 (21%)	n.d	n.d
DeNardis 2008	56	n.d	11 (20%)	11 (20%)	n.d	n.d
Bell 2008	40	(0%)	3 (7.5%)	3 (7.5%)	n.d	n.d
Hoekstra 2009	32	2 (6.2%)	4 (13%)	6 (19%)	n.d	n.d

*In our studies, one patient may have >1 intra-operative or/and post-operative complication

Conversions and several complications may delay the discharge of the patient. The number of conversions, intraoperative complications and early postoperative complications, was low in robotic-assisted operations. Recovery was fast, and in Studies I, II and IV the median hospital stay was 1, 1 and 2 days, respectively. In study II were no significant differences in the length of inpatient stay between traditional and robotic-assisted laparoscopy. However, in the whole study population, no patient was discharged on the day of the operation In North American studies on same day discharge, 78% of patients operated for benign (53%) or malignant (47%) indications were discharged on the day of surgery (Lee, Calderon et al. 2014). In the study of Penner et al., the rate was as high as 84%. They did not find any significant difference in complications during the next 2 weeks, or in seeking hospital treatment compared to surgical patients that were monitored overnight (Penner, Fleming et al. 2015). Although the high rate of same day discharge in the American studies may at least partly be a reflection of the different health care system as compared to the nationalized Finnish system, the same day discharge could be an option in selected cases even in Finland.

5.2 Costs of robotic-assisted versus traditional laparoscopy

As expected, robotic-assisted surgery turned out to be more expensive than traditional laparoscopic surgery (Study III). When including complications, the median total costs were EUR 7,983 vs. EUR 5,823, or 37% in favor of traditional laparoscopy. Without the complications, the cost for robotic-assisted surgery was 35% higher (EUR 1,928) per operation. However, the conversions in the traditional group did have a significant impact on the total costs. Because of longer recovery room times and inpatient stays, the costs caused by the conversions nearly equaled the costs of the robotic-assisted operations. Robotic-assisted surgery should thus be favored in demanding operations with a high risk of conversion, and in operations that could not otherwise be performed mini-invasively, such as operations on very obese women.

International comparisons between the costs of robotic-assisted and traditional laparoscopy are somewhat problematic because healthcare systems operate differently in various countries. E.g. a French study found that, in the treatment of patients with endometrial carcinoma, the cost of traditional laparoscopy is EUR 2,733 and the cost of robotic-assisted surgery is EUR 7,402. When other treatment costs were included in the calculations, the cost was EUR 6,666 vs. EUR 10,816, i.e robotic-assisted surgery was 62% more expensive than traditional laparoscopy, and also markedly more expensive than robotic-assisted surgery in our Study III (Desille-Gbaguidi, Hebert et al. 2013). The latter difference may be explained at least partly by a difference in postoperative inpatient stay (4-5 vs. 1-2 days).

However, our results seem to be in line with studies conducted in the U.S., which found that robotic-assisted laparoscopy is 17–33% more expensive than traditional laparoscopy (Barnett, Judd et al. 2010, Wright, Ananth et al. 2014).

The biggest cost items in robotic-assisted laparoscopy are the instruments, as well as the amortization and maintenance costs of the robot (Barnett, Judd et al. 2010, Wright, Ananth et al. 2014, Lönnerfors, Reynisson et al. 2015, Schreuder, Verheijen 2009, Reynisson, Persson et al. 2013). This was also the case in the present study. In the robotic group, instruments were the highest cost item per operation (Md. robot EUR 1,813 vs. traditional EUR 214) The amortization costs of the robot and the OR time were in second largest item (Md. robot EUR 1,172 vs. traditional EUR 232). In practice, these factors explain the cost difference between robotic-assisted and traditional surgery but they are difficult to influence at present. In the future, competition may hopefully drive the costs of robotic-assisted surgery down.

High operating costs can be compensated with shorter OR times, which decrease the total costs. In Study II, OR time was significantly shorter in the robotic-assisted laparoscopy. In addition, effective use of the robot would drive the cost per operation down.

In robotic-assisted surgery, the fast discharge of patients and a small number of instant complications were significant in terms of reducing costs, as well as a short OR time. On the other hand, robotic-assisted laparoscopy was associated predominantly by postoperative complications that delayed recovery, and some of the patients had to return to the hospital. The net effect was that the cost of the robotic-assisted surgery was 35% more expensive without complications, while it was 37% more expensive with complications included.

5.3 Strengths and weaknesses of the study

A strength of Study I is that two surgeons performed all operations during the implementation phase of the robotic-assisted surgery, and that the learning curves were established for both on the exactly same type of operation, or LH+BSO+PLND. A weakness of Study I was that we did not specify how different surgical stages were learned at the console.

The greatest strength of Study II is its randomized nature. To our knowledge, this is the first randomized controlled trial ever conducted on the implementation of robotic-assisted surgery in gynecologic oncology. A weakness of the randomized Study II is its relatively small sample size. In order to detect at least a 25% difference between the study arms, 100 patients needed to be recruited. Even material of this size took approximately 3 years to collect. During the recruitment phase of the study, clinical guidelines for endometrial carcinoma were amended: PALND instead of PLND for high-risk endometrial carcinoma patients was now recommended. Because of this, some of the patients were no longer suitable for the randomized study. They were assigned for robotic-assisted surgery including para-aortic lymphadenectomy, which slowed the recruitment. This change also made the study results perhaps less interesting to the gynecologic oncology community, because the surgical model could no longer be applied directly to the current surgical guidelines.

A strength of Study III is that it was possible to find the true costs reliably in the Hospital Management Information System. A weakness is that the power the calculations were not made for the costs, but rather for the clinical outcome or the operation time (Study II).

The strengths of Study IV are the big sample size and the fact that surgeons used the same technique in PALND during the whole study period. A weakness of Study IV is that the lymph nodes above and below the IMA were not studied separately. It would have been interesting to know the number of lymph node metastases above the IMA level. It is considerably easier to remove lymph nodes above the IMA using robotic-assisted laparoscopy than traditional laparoscopy, and the information could have had an effect on the future comparison and selection of surgical techniques.

An important strength of all sub-studies is the meticulous recording and collection of the data. The classification of complications was difficult and complex. It would be easier to compare the number of complications across the studies if a uniform classification was used, e.g. the Clavien-Dindo classification (Dindo, Demartines et al. 2004)

5.4 Future of the robotic-assisted surgery

In the future, traditional 3D laparoscopy will become more common, and it might challenge the robotic-assisted technique. In traditional 3D laparoscopy, manipulation of tissue is easier, and so is suturing compared to traditional 2D laparoscopy. However, the small instrument tips that move well and extensively and can be moved with wrist movements remain the unsurpassed benefit of the robotic-assisted technique. Fatigue and tireless of hands, extra trembling and unnecessary camera movements do not interfere with robotic-assisted operations, and the surgeon can better focus on the main task, i.e. operating on the patient. Gynecological cancer operations are often long, and good ergonomics of the console is essential for successful operations. These are the factors that result in good patient safety of robotic-assisted laparoscopy and important reasons to the fact that the number of intraoperative complications is low in robotic-assisted laparoscopy.

Based on this study, it can be said that robotic-assisted surgery is excellently suited for gynecological cancer operations. Robotic-assisted laparoscopy is fast, of high-quality and safe. Centralization of operations and thus arranging a sufficient number of operations per surgeon is rational and helps to achieve good results.

Out of gynecological cancer operation types, the number of robotic-assisted pelvis exenterations and radical trachelectomies for cervical cancer may increase in the future. Robotic-assisted surgery would also be well suited for challenging benign gynecological surgery, such as for rectovaginal and urinary tract endometriosis. If the competition will in the future decrease the costs of robotic technique, the spectrum of indications for robotic-assisted surgery may broaden. The new and future versions of the robot have and will have clear benefits as compared to the old model: e.g. the camera can be turned towards the upper abdomen. This widens the range of potential operation types, because the procedure can be performed similarly as with the DD technique, but without removing the robot and turning the patient. The new innovations will probably shorten the operation set-up time, further decrease the OR time and cut the costs.

6 SUMMARY AND CONCLUSIONS

The main findings and conclusions of the study were:

1. The learning curve for robotic-assisted laparoscopy is short in a hospital with laparoscopic experience. The operation time stabilizes after ten operations.

2. Robotic-assisted laparoscopy is faster than traditional laparoscopy in operations for endometrial carcinoma. Also, the operating room time is shorter in robotic-assisted surgery than in traditional laparoscopic surgery. There is no significant difference in the surgical outcome between robotic-assisted and traditional laparoscopy.

3. Robotic-assisted laparoscopy is 35% more expensive than traditional laparoscopy in the treatment of endometrial cancer. The cost difference is mainly explained by amortization of the robot and its instrumentation.

4. The transperitoneal robotic-assisted technique seems to be well suited for laparoscopic high para-aortic lymphadenectomy. Para-aortic lymphadenectomy can be performed successfully to high level or above IMA in 83%, and up to renal vessels in 24% of the patients. The number of removed para-aortic lymph nodes increases as the surgeon gains more experience, and the learning curve still changes after 40 procedures.

5. Robotic-assisted procedures are well suited for gynecological surgery and are safe to perform. In addition to a shortening of the operation time, the number lymph nodes removed increased after the learning curve. Conversions to open surgery were few and the rate of intraoperative complications was minimal. For patients with high risk endometrial cancer and cervical cancer, robotic-assisted laparoscopic surgery is an ideal option.

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Minna Mäenpää

Minna Mäenpää

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9 ORIGINAL COMMUNICATIONS

AOGS
ACTA Obstetricia et Gynecologica Scandinavica

AOGS MAIN RESEARCH ARTICLE

Implementing robotic surgery to gynecologic oncology: the first 300 operations performed at a tertiary hospital

MINNA MÄENPÄÄ[1], KARI NIEMINEN[1], EIJA TOMÁS[1], TIINA LUUKKAALA[3] & JOHANNA U. MÄENPÄÄ[1,2]

[1]*Department of Obstetrics and Gynecology, Tampere University Hospital, Tampere,* [2]*School of Medicine, University of Tampere, Tampere, and* [3]*Science Center, Pirkanmaa Hospital District and School of Health Sciences, University of Tampere, Tampere, Finland*

Key words
Learning curve, robotic-assisted laparoscopic surgery, endometrial cancer, operative time, lymphadenectomy, lymph node, gynecology

Correspondence
Minna Mäenpää, Tampere University Hospital, Department of Obstetrics and Gynecology, P.O. Box 2000, FI-33521 Tampere, Finland.
E-mail: minna.maenpaa@pshp.fi

Conflict of interest
Kari Nieminen is a proctor for robotic surgery. The other authors have stated explicitly that there are no conflicts of interest in connection with this article.

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Abstract

Objective. To investigate the initial experience with robotic-assisted laparoscopic surgery in gynecologic oncology. *Design.* A retrospective survey. *Setting.* Tertiary referral center. *Population.* The first 300 patients operated on using robotic assistance at the Department of Obstetrics and Gynecology of Tampere University Hospital, from March 2009 through January 2013. *Methods.* Retrospective patient chart review. *Main outcome measures.* The primary outcome measure was the learning curve events, and the complication and conversion rates were secondary outcome measures. *Results.* The commonest type of operation was hysterectomy, bilateral salpingoophorectomy and pelvic lymphadenectomy (LH + BSO + PLND, $n = 89$), followed by the same procedure amended by para-aortic lymphadenectomy (PALND, $n = 74$), type II radical hysterectomy ($n = 24$), and PLND + PALND ± omentectomy ($n = 15$). A learning curve was most evident for LH + BSO + PLND: whereas the median operative time of all 89 operations was 167 min (range 403–104), it was 260 (range 403–135) and 153 (range 247–104) min in the case of the first and last 20 operations, respectively. The learning curve was short, or 10 procedures. A learning curve was also seen for the preoperative time in the operation room and for the number of lymph nodes harvested. The median blood loss during all 300 operations was 100 mL (range 5–3200). The median postoperative hospital stay was 1 day. The conversion rate was 4.0%, and the complication rate 19.3% (major in 9%). *Conclusion.* The learning curve of robotic-assisted laparoscopic surgery appears to be short, or 10 operations. Robotic-assisted procedures seem to offer a safe and useful alternative to traditional techniques.

Abbreviations: BSO, bilateral salpingoophorectomy; LH, hysterectomy; PALND, para-aortic lymphadenectomy; PLND, pelvic lymphadenectomy.

Introduction

Robotic-assisted laparoscopic surgery has recently been welcomed with enthusiasm by the gynecologic community, especially for oncologic indications. The advantages of robotic-assisted surgery as opposed to conventional laparoscopy have been purported to include the three-dimensional view, a better and more precise visibility of the operative field, the fatigue-resistant properties of robot

> **Key Message**
>
> The learning curve of robotic-assisted surgery is short, or approximately 10 operations, provided that the whole operative team is dedicated.

hands, as well as a better mobility and greater range of movement of the instrument head. This results potentially in a more precise technique and reduced tissue damage (1,2).

The advantages of the mini-invasiveness are tangible: reduced bleeding and a smaller risk of complications, and a faster recovery from the surgery, all of which provide benefits in the form of a shortened hospital stay and shorter sick leaves (3–6). In gynecology, patients with cancer have received the greatest benefit from robotic surgery (7). The most important patient groups have been the ones with endometrial cancer, those that require a staging operation for the confirmation of an apparent early stage ovarian cancer, and patients with cervical cancer who would previously have been operated on with open surgery (6,8–10).

At present, the only available robot is the da Vinci Surgical System (11) The learning curve with it is faster (4,12,13) than in conventional laparoscopy. In particular, the endoscopic stitching procedure can be adopted much more quickly by the surgeon compared with conventional methods (11,14).

At our institution, the first robotic-assisted operation for a gynecological patient was performed in March, 2009. The aim of this study was to review the initial experience with the new surgical system, with a special emphasis on operative learning curves. This study covered the total operation time and the time spent on the various preparation phases, respectively.

Material and methods

The data collected for this study includes the first 300 robotic-assisted operations performed at the Department of Obstetrics and Gynecology of Tampere University Hospital, from March 2009 through January 2013. The median age of the patients was 62 years (range 20–88), and their median body mass index was 28 kg/m^2 (range 17–77). Of the 300 operations (Table 1), 58 were done for benign indications and 242 for cancer (196 endometrial, 30 cervical, and 16 ovarian and Fallopian tube carcinomas, respectively). A majority (76%) of the carcimomas were of FIGO Stage I.

The study was approved by the local Ethics Committee (ETL R13157). No informed consent was obtained from the patients because this was a retrospective and descriptive study based on the patient records.

The operations (an average of two operations a week) were all performed by three gynecologic surgeons. Two surgeons started the operations and a third one joined the team after the first 100 operations. Surgeon A conducted 196 operations as the primary surgeon and the other surgeons the remaining 104 operations (B 50 and C 54, respectively). The tasks of the secondary surgeon were performed by the same team. The nursing team consisted of three qualified operation room nurses, who alternated as instrument, anesthetic and passer nurses, respectively. For the first 20 operations, the anesthesiologist in charge was recruited from the general staff of the hospital, and during the remaining 280 operations, experienced senior anesthesiologists took care of the patients.

Table 1. The types of operations done with robotic surgery at Tampere University Hospital

Type of operation	*n*	%
LH + BSO + PLND	89	29.7
LH + BSO + PLND + PALND ± omentectomy	74	24.7
Type II radical hysterectomy	24	8.0
PLND, PALND ± omentectomy	15	5.0
PLND	5	1.7
Other staging procedures	19	6.3
LH + BSO	34	11.3
Others[a]	40	13.3
Total	300	100

BSO, bilateral salphingoopherectomy; LH, laparoscopic hysterectomy; PALND, para-aortic lymphadenectomy; PLND, pelvic lymphadenectomy.
[a]Myoma enucleations (*n* = 21), operations for endometriosis (*n* = 6), corrective procedures for cesarean section scars (*n* = 4), radical trachelectomy (*n* = 2), sacrocolpopexy (*n* = 3), extirpation of cervical stump (*n* = 2), intra-abdominal setting of cerclage (*n* = 1), removal of para-aortic metastasis (*n* = 1).

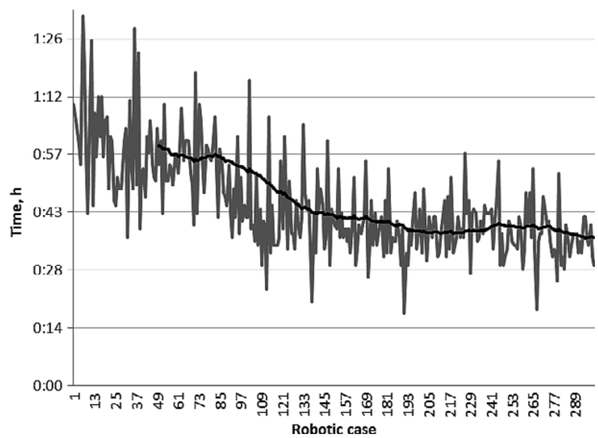

Figure 1. The preoperative preparation time with moving average of 50 patients at Tampere University Hospital.

The primary outcome measure was the learning curve events: preparation time, docking time and overall operation time (skin to skin), respectively, which were calculated for each operation. The learning curves were constructed separately for different surgeons and for different types of operation.

Distributions of time values were shown by medians with interquartile ranges and/or ranges. In Table 4 the means with standard deviations are also shown, to facilitate comparisons with previous reports. Differences between first and last operations were tested by Mann–Whitney test. Statistical analyses were performed using IBM SPSS Statistics version 20 (IBM Corp., Armonk, NY, USA).

The secondary outcome measures included the amount of bleeding, intraoperative complications and conversions, as well as the length of postoperative stay, and the number of lymph nodes harvested.

Results

The median time that elapsed from the arrival of the patients to the operation room and the start of the operation was 42 min (range 18–92). For the first 50 patients this

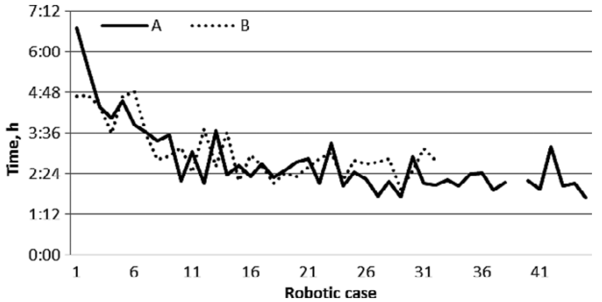

Figure 2. Hysterectomy, bilateral salpingoophorectomy and pelvic lymphadectomy: skin- to skin operation time [median 167 min (range 104–403)]. A, surgeon A; B, surgeon B.

was significantly longer than for the 50 last patients ($p < 0.001$), or 58 (range 37–92) min versus 36 (range 19–54) min, respectively (Figure 1). The median time between the start of the operation and the start-up of the robotic console was 25 min (range 14–98), with no clear shortening over the study period. However, the median docking time, which was 7 min (range 1–35) for all 300 operations, shortened with increasing experience: the difference between the first and last 50 operations was significant [9 min (range 3–25) and 6 min (range 1–16), respectively; $p = 0.003$].

The commonest type of operation was hysterectomy (LH), bilateral salpingoophorectomy (BSO) and pelvic lymphadenectomy (PLND) for endometrial cancer, accounting for nearly a third, or 89, of the operations. For this type of operation, the learning curve for operation time was the most eminent (Figure 2): the first operation took 6 h 43 min to perform whereas the last one lasted only 1 h 44 min. The learning curve was very similar for both surgeons (A and B) who alternated at the console, with the most significant decrease over the first 10 operations. The median times of the first 10 and last 10 operations were 243 (range 135–403) min and 132 (range 104–198) min (surgeon A), and 243 (range 179–294) min and 174 (range 120–197) min (surgeon B), respectively ($p < 0.001$ for both).

The effect of training was reflected also in the number of pelvic lymph nodes harvested. Thus, the number of

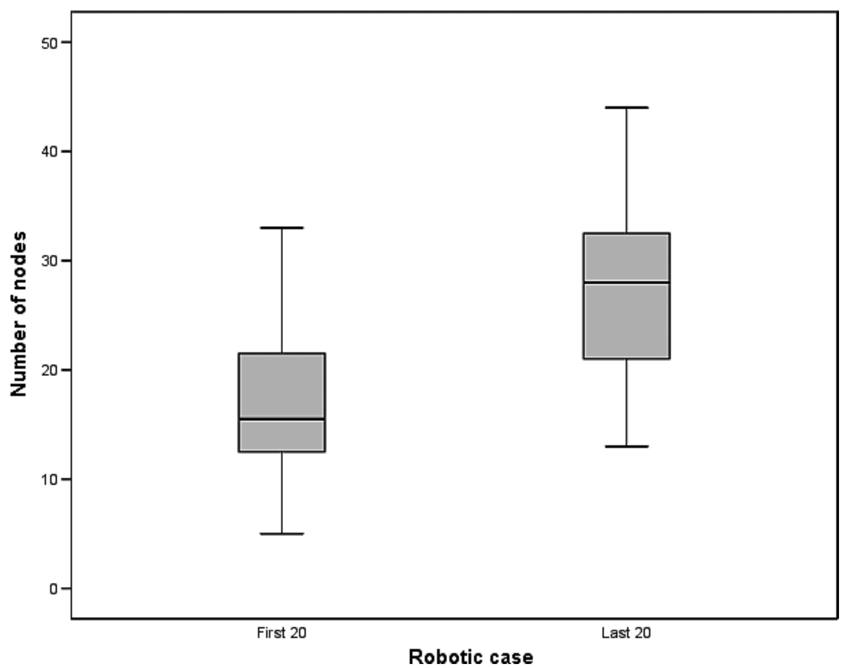

Figure 3. The number of pelvic lymph nodes surgeon A removed during his first and last 20 low-risk endometrial cancer operations. Number of nodes were shown by medians (black line), interquartile ranges 25–75 centiles (box) and ranges (line bar).

Table 2. Conversions and re-operations in connection with robotic surgery

	n	%
Reasons for conversions		
Adhesions	6	
Bleeding[a]	2	
Disseminated cancer	1	
Limited visibility	2	
Technical problem with the robot	1	
Total	12	4.0
Reasons for re-operations		
Bleeding[b]	3	
Peritonitis	1	
Intestinal herniation	1	
Vaginal cuff dehiscence	3	
Total	8	2.7

[a]The bleeding sites: uterine myoma bed, uterine artery.
[b]Two from uterine artery and inferior mesenteric artery.

Table 3. Intra-operative, early and late complications during robotic surgery at Tampere University Hospital

	n	%
Intra-operative complications		
Vascular injury and bleeding	7	
Bowel perforation	1	
Vaginal wall laceration	1	
Total		12.8
Early postoperative complications (<7 days)		
Intra-abdominal bleeding/hematomas	5	
Port-site hematomas	2	
Respiratory insufficiency	2	
Atrial fibrillation	1	
Miscarriage[a]	1	
Peritonitis	1	
Total		17.1
Late postoperative complications (>7 days)		
Wound/urinary tract infection	15	
Pelvic infection	13	
Vaginal cuff hematoma, defective healing	6	
Lymph leakage/cyst	7	
Cardio-pulmonary	3	
Nerve injury	1	
Intestinal herniation	1	
Vaginal cuff dehiscence	3	
Total		70.0
Total number of complications[b]	70	100

Twenty-seven patients (9.0%) had major complications.
[a]The miscarriage took place immediately after the insertion of an abdominal cerclage performed at 12^{+5} weeks of gestation.
[b]A total of 58 patients had complications (19.3%), of whom 11 had several complications.

lymph nodes removed increased as the number of operations performed by the same surgeon increased. Surgeon A performed most of the low-risk endometrial cancer operations (LH + BSO + PLND), and a learning curve as related to the number of lymph nodes removed was estimated for him (Figure 3). In the first and last 20 patients, the median number of lymph nodes harvested was 16 (range 5–33) and 28 (range 13–44), respectively. The difference was significant ($p < 0.001$).

In the case of the staging procedures [LH + BSO + PLND + para-aortic lymphadenectomy (PALND) ± omentectomy] the learning curve was less evident than in the case of LH+BSO+PLND. In type II radical hysterectomy, a short learning curve is seen over the first seven operations. However, the first 10 operations did not last significantly longer than the 10 last operations ($p = 0.529$).

A total of 213 pelvic and 98 para-aortic lymphadenectomies was performed, respectively, for 217 patients. The respective median number of pelvic and para-aortic lymph nodes removed was 22 (range 0–57) and 11 (range 0–38). Interestingly, more pelvic lymph nodes (median 27, range 13–57) were removed during type II radical hysterectomy operations than during other operations, probably reflecting the enhanced exposure of the pelvic side wall.

Lymph node metastases were found in 23 of 217 (10.6%) patients lymphadenectomized. Twelve patients had metastases in pelvic nodes, eight in para-aortic nodes, and three in both. Of the 352 and 162 pelvic and para-aortic nodes removed, 38 (10.8%) and 25 (15.4%) respectively were metastatic. All metastatic nodes were found in patients with high risk endometrial carcinoma, cervical cancer or ovarian cancer. None of the patients with low-risk endometrial carcinoma had lymph node metastases.

Twelve (4.0%) conversions to laparotomy were done, and in five cases major re-operations (laparotomy in four and laparoscopy in one) had to be performed (Table 2). A total of 58 (19.3%) patients had complications, most of which were infectious in nature (Table 3). About half of the infections needed to be treated with intravenous antibiotics. Eleven patients had more than one complication, and 27 (9%) patients had major complications. The major complications included vascular and bowel injuries, major bleeding and hematoma, infection requiring intravenous antibiotics, with or without an abscess formation, pulmonary failure and embolism, myocardial infarction, vaginal cuff dehiscence, and a miscarriage. No postoperative deaths occurred during the study period.

The median amount of bleeding was 100 mL (range 5–3200). The median length of the postoperative hospital stay was 1 day (range 1–10). However, in the case of operations converted to laparotomy, the median length of the postoperative hospital stay was 6 days (range 3–31).

A more detailed information on the 134 operations performed for endometrial carcinoma (LH + BSO

Table 4. Summary of studies on robotic-assisted surgery for endometrial cancer

Study	*n*	Statistics	Age	BMI	Length of operation (min)	Pelvic nodes	PA nodes	Blood loss (mL)	Hospital stay (day)	Conversion rate (%)	Complication rate (%)
Veljovich et al. (23)	25	Md (range)	60 (36–85)	28 (19–49)	283 (171–443)	17.5 (2–32)	n.d.	67 (10–300)	1.7 (0.7–9.0)	n.d.	20
Bell et al. (26)	40	Mean ± SD	63 ± 10.1	33 ± 8.5	184.0 ± 41.3	17 ± 7.8	n.d.	166 ± 226	n.d.	n.d.	7.5
DeNardis et al. (27)	56	Mean ± SD	59 ± 10	29 ± 6.5	177 ± 55	13.3 ± 8.6	6.5 ± 4.4	105 ± 77	1.0 ± 0.5	5.4	19.7
		Range		19–46	80–307			25–500			
Boggess et al. (28)	103	Mean ± SD	62 ± 10.6	33 ± 7.6	191.2 ± 36.0	20.5 ± 13.6	12.0 ± 9.0	75 ± 101	1.0 ± 0.2	2.9	5.8
Lowe et al. (9)	405	Mean ± SD	62	32	170.5 ± 68.9	12.7 ± 8.4	2.8 ± 3.1	88 ± 97	1.8 ± 2.8	6.7	18.1
		Md			172	12	2	50	1.0		
		IQR			119–210	7–18	0–5	25–100	1.0–2.0		
Seamon et al. (17)	79	Mean	60	32	241.5	21.3	9.8	99	1.5	12.4	10.1
Hoekstra et al. (29)	32	Md (range)	62	29 (21–54)	195	17	n.d.	50	n.d.	3.1	18.8
Cardenas-Goicoechea et al. (21)	102	Mean ± SD	62 ± 8.7	32 ± 8.1	237 ± 57	13 ± 6.8	9 ± 6.1	109 ± 83	1.9 ± 1.67	1.0	26.5
		Md (range)	61 (40–84)	31 (17–55)	222 (130–437)	13 (0–50)	9 (0–27)	100 (25–400)	1 (1–14)		
Paley et al. (30)	377		n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	3.5	9.9
Present study[a]	134	Mean ± SD	68 ± 9.8	30 ± 6.1	197 ± 58.7	21.8 ± 9.7	11.5 ± 6.4	150 ± 278	2.0 ± 1.6	2.2	19.4
		Md (range)	68 (41–86)	30 (20–46)	183 (104–403)	20 (5–51)	10 (0–28)	100 (10–3000)	2 (1–10)		
		IQR	61–75	25–33	153–229	14–28	7–16	50–188	1–2		

n.d., no data; SD, standard deviation; Md, Median; IQR, interquartile range; LH, laparoscopic hysterectomy, BSO, bilateral salphingoopherectomy, PLND, pelvic lymphadenectomy; PALND, para-aortic lymphadenectomy.

[a]LH + BSO + PLND ± PALND.

+ PLND ± PALND) is given in Table 4, along with data gathered from previous studies for comparison.

Discussion

Preparatory measures in robotic-assisted laparoscopic surgery differ from the ones in conventional laparoscopic surgery in that they also include docking, or attaching the robotic arms to the trocars. Thus, a learning curve study should address also the preoperative period at the operation room; this, however, seems to be largely ignored in the previous literature. In the present study, the total time spent in the operation room before the operation started decreased by 22 min between the first and last 50 operations, or from a median of 58 to a median of 36 min, respectively. This phenomenon reflects the importance of training of the whole operative team and not only the surgeons, when aiming for a more effective use of operative resources of a hospital.

Of the different types of operation, the learning curve was most evident in the case of LH + BSO + PLND, or the commonest type. Excluding the very first cases, the learning curves of surgeons A and B for this operation were almost identical, 10 operations (Figure 2). These learning curves fall into the lower end of the spectrum presented in the literature. Lowe et al. (9) performed a multicenter study involving 405 staging operations for endometrial cancer and different surgeons, and found out that the fastest adaptation took place during the first 9–20 cases. In the study of Tahmasbi et al. (15), the length of the learning curve was nine operations in cervical and endometrial cancer staging operations. Seamon et al. (16,17) reported the learning curves of two surgeons performing surgery for endometrial cancer. In their study, the learning curve was somewhat longer, 20 operations. However, a learning curve can be significantly longer, as in the study of Lenihan et al. (18), who reported the length of learning curves for benign gynecologic surgery, mainly hysterectomies, to be 50 operations. The relative short learning curve presented here may reflect the fact that already since the late 1990s, about 75% of hysterectomies and pelvic lymphadenectomies for endometrial cancer had been performed laparoscopically at our institution (19).

In the case of staging operations for ovarian cancer, a learning curve was more difficult to detect. It is likely that the surgeons had already familiarized themselves with the robotic-assisted technique while performing the operations for endometrial cancer to the point that no further significant progress was to be expected for these very similar procedures. However, in the case of radical hysterectomy for cervical cancer, the transition to robotic-assisted surgery took place directly from laparotomy, and not via conventional laparoscopy. Consequently, a slight learning curve over seven patients is seen.

An effect of training was evident also in the number of lymph nodes harvested (Figure 3). A similar trend was also seen in the study of Holloway et al. (20). They compared the first and last 10 operations and found out that the mean number of lymph nodes removed increased from 15.0 and 4.7, to 21.0 and 8.0 in the pelvic and paraaortic areas, respectively. However, in the majority of the studies this phenomenon has not been seen (4,17,21). Of note is that no lymph node metastases were found in patients with low-risk endometrial carcinoma, which is evidence in favor of the recently adopted practice to refrain from lymphadenectomy for these patients (22).

A summary of studies on robotic-assisted surgery for endometrial carcinoma is given in Table 4. The present series seems to compare well in relation to the variables studied, and the rate of serious complications was very low. The area of the external iliac vein has been found to be the most vulnerable one in robotic-assisted gynecologic operations (9,23). We had two cases of significant bleeding in that area. Both cases were successfully treated laparoscopically with clips. Three additional cases of major bleeding occurred: one after myoma enucleation, one bleeding from the inferior mesenteric artery, and one from the uterine artery. These complications required a laparotomy. Three patients, or 1.4% of the hysterectomized patients, had a postoperative vaginal vault dehiscence (two after an LH and one after radical hysterectomy). According to the literature, the rate of vault dehiscence has been 0–10% following simple and 6% following radical robotic-assisted hysterectomy, respectively (24,25).

In conclusion, robotic-assisted laparoscopic surgery can be learned quite fast, after the first 10 patients, provided the operative team is already experienced in conventional laparoscopy. Robotic-assisted procedures seem to offer a safe and useful alternative to conventional surgical techniques.

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GYNECOLOGY

Robotic-assisted vs traditional laparoscopic surgery for endometrial cancer: a randomized controlled trial

Minna M. Mäenpää, MD; Kari Nieminen, PhD; Eija I. Tomás, PhD; Marita Laurila, MD; Tiina H. Luukkaala, MSc; Johanna U. Mäenpää, PhD

BACKGROUND: Previous studies comparing robotic-assisted laparoscopic surgery to traditional laparoscopic or open surgery in gynecologic oncology have been retrospective. To our knowledge, no prospective randomized trials have thus far been performed on endometrial cancer.

OBJECTIVE: We sought to prospectively compare traditional and robotic-assisted laparoscopic surgery for endometrial cancer.

STUDY DESIGN: This was a randomized controlled trial. From December 2010 through October 2013, 101 endometrial cancer patients were randomized to hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymphadenectomy either by robotic-assisted laparoscopic surgery or by traditional laparoscopy. The primary outcome measure was overall operation time. The secondary outcome measures included total time spent in the operating room, and surgical outcome (number of lymph nodes harvested, complications, and recovery). The study was powered to show at least a 25% difference in the operation time using 2-sided significance level of .05. The differences between the traditional laparoscopy and the robotic surgery groups were tested by Pearson χ^2 test, Fisher exact test, or Mann-Whitney test.

RESULTS: In all, 99 patients were eligible for analysis. The median operation time in the traditional laparoscopy group (n = 49) was 170 (range 126-259) minutes and in the robotic surgery group (n = 50) was 139 (range 86-197) minutes, respectively ($P < .001$). The total time spent in the operating room was shorter in the robotic surgery group (228 vs 197 minutes, $P < .001$). In the traditional laparoscopy group, there were 5 conversions to laparotomy vs none in the robotic surgery group ($P = .027$). There were no differences as to the number of lymph nodes removed, bleeding, or the length of postoperative hospital stay. Four (8%) vs no (0%) patients ($P = .056$) had intraoperative complications and 5 (10%) vs 11 (22%) ($P = .111$) had major postoperative complications in the traditional and robotic surgery groups, respectively.

CONCLUSION: In patients with endometrial cancer, robotic-assisted laparoscopic surgery was faster to perform than traditional laparoscopy. Also total time spent in the operation room was shorter in the robotic surgery group and all conversions to laparotomy occurred in the traditional laparoscopy group. Otherwise, the surgical outcome was similar between the groups. Robotic surgery offers an effective and safe alternative in the surgical treatment of endometrial cancer.

Key words: endometrial cancer, gynecologic surgery, operation time, robotic-assisted surgery, traditional laparoscopic surgery

Introduction

Endometrial carcinoma is globally the sixth most common cancer in women, with 320,000 new cases annually, or 4.8% of cancers in women. The estimated age-standardized incidence rate (World standard) is 8.3 per 100,000 women. The highest incidence rates are found in North America (19.1 per 100,000) and Northern and Western Europe (12.9-15.6 per 100,000). The rates are low in South-Central Asia (2.7 per 100,000) and in most parts of Africa (<5 per 100,000).[1] In developed countries, endometrial cancer is diagnosed often (80%) at International Federation of Gynecology and Obstetrics stage I and can thus be cured by surgery, albeit followed by adjuvant therapy if high-risk features are encountered.[2] Over the last 20 years, laparotomy has been replaced by minimally invasive laparoscopic techniques, of which robotic-assisted surgery has lately become increasingly popular.[3]

The advantages of robotic-assisted surgery as opposed to conventional laparoscopy have been described in retrospective and observational studies.[4] The 3-dimensional view, the better and more precise visibility of the operation area, the fatigue-resistant properties of robot hands, as well as the better mobility and the greater range of movement of the instrument head all facilitate working with the robot. Because of these advantages, the learning curve is faster than in conventional laparoscopy[5-8]; eg, endoscopic suturing technique can be adopted faster.[9] Based on the advantages presented above, robotic-assisted surgery has been adopted widely as the operative treatment of endometrial cancer, but as far as we are aware, it has not been tested in a randomized, controlled setting. The present study was initiated in December 2010 to answer to this obvious unmet need.

Materials and Methods

A total of 101 patients scheduled for laparoscopic hysterectomy, bilateral salpingo-oophorectomy (BSO), and pelvic lymphadenectomy (PLND) at the Department of Gynecology and Obstetrics of Tampere University Hospital were randomized preoperatively to undergo either robotic-assisted (da Vinci S Surgical System; Intuitive Surgical Inc, Sunnyvale, CA) or conventional laparoscopic operation from December 2010 through October 2013 (Figure 1). Only 1 patient refused to participate in the study.

Women eligible to the study had a low-grade (grade 1-2) endometrial

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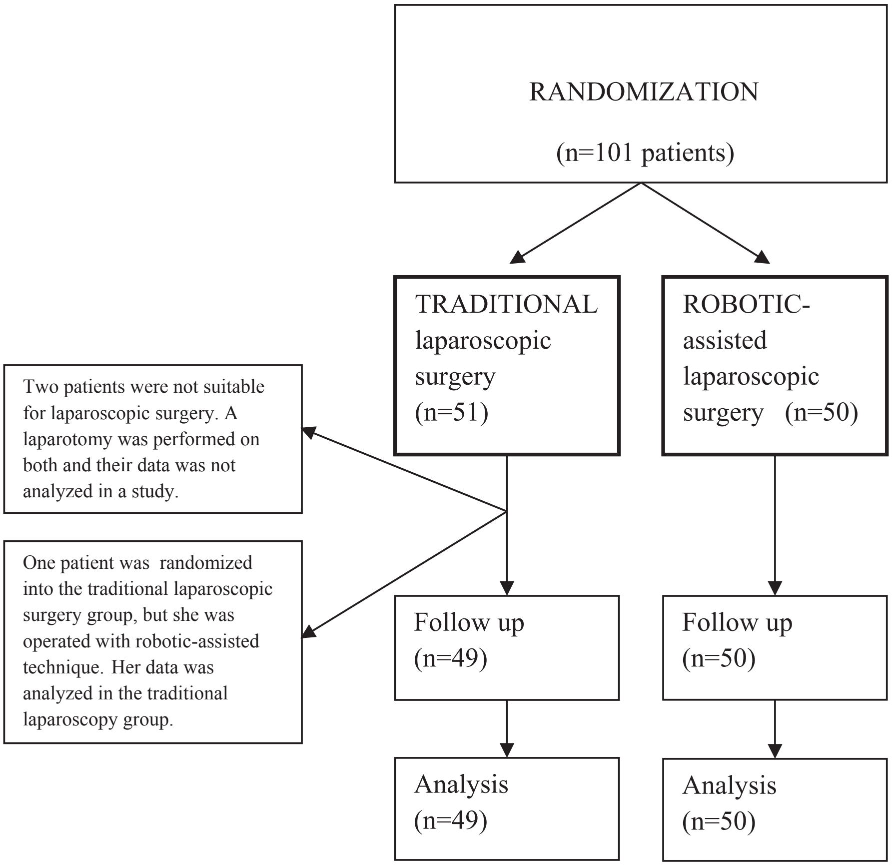
FIGURE 1
Flow chart of study



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carcinoma, and were scheduled for laparoscopic surgical staging, ie, for a laparoscopic hysterectomy along with BSO and PLND. The study exclusion criteria included a narrow vagina or a uterus too large to be removed through vagina, and the patient's condition not allowing for a deep Trendelenburg position (Figure 1). The operations were all performed by gynecologic oncologists with several years of experience with laparoscopic surgery. Thus, a learning curve was not included in the operations. The patients were randomized to undergo either traditional or robotic-assisted laparoscopic surgery, and were stratified for overweight (body mass index [BMI] <30 and ≥30) and age (<65 and ≥65 years). The randomization was made with the minimization software for allocating patients to treatments in clinical trials (MINIM, Version 1.5/28-3-90, by S. Evans, P. Royston, and S. Day [https://www-users.york.ac.uk/~mb55/guide/minim.htm]).

The surgical techniques (Table 1) differed between the groups in the insertion of trocars, entering the abdominal cavity, and closing the vagina. PLND was performed in the same way in both groups: The external iliac artery was skeletonized up to the bifurcation of the common iliac artery into the external and internal iliac arteries. The obturator lymph nodes were removed from the area between the obturator nerve and the external iliac vein. As antithrombotic prophylaxis, all patients were given low-molecular-weight-heparin and were wearing antithrombotic stockings. Cefuroxime was used as primary antibiotic prophylaxis, combined with metronidazole when indicated, and replaced with levofloxacin in case of cephalosporin allergy. A cytological sample from the pouch of Douglas was obtained from all patients.

The operative specimens were otherwise processed and evaluated as part of the hospital routine practice, but an experienced gynecopathologist (M.L.) reviewed all lymph node samples. The relevant gynecologic and medical histories of the patients can be found in Table 2. The patients' hemoglobin level was measured preoperatively and postoperatively. By definition, a decrease in the hemoglobin level >40 g/L, and need of transfusion or estimated blood loss >500 mL were regarded as a bleeding complication. Early postoperative complications took place before discharge and late complications following discharge but during the next 6 months. Major infection required intravenous antibiotics and minor wound or urinary tract infection oral antibiotics.

Written informed consent was obtained from the study participants. The study was approved by the Ethics Committee of Tampere University Hospital (identification number ETL R10081). The trial was registered at ClinicalTrials.gov, www.clinicaltrials.gov, NCT014 66777.

Statistical plan

The primary outcome measure was overall operation time (skin to skin; time from the first incision to the last suture). The study was powered to show at least a 25% difference in operation time using 2-sided significance level of .05. For this, at least 45 patients were needed in each treatment arm to achieve a power of 0.80.[10] The secondary outcome measures included the total time spent in the operating room, number of lymph nodes harvested, intraoperative complications and conversions, amount of bleeding, length of postoperative stay, and postoperative pain scale.

The differences between traditional laparoscopy and robotic surgery groups were tested by Pearson χ^2 test, Fisher exact test, or by Mann-Whitney and/or independent samples t test. The statistical analyses were performed using software (SPSS Statistics, Version 23; IBM Corp, Armonk, NY). P values

TABLE 1
Surgical techniques

	Traditional	Robot
Entering abdominal cavity	Veress needle or open technique through umbilicus	Open technique
Size and placement of trocars	10 mm for Camera in umbilicus, two 5 mm lateral to both epigastric arteries, 12 mm in midline above symphysis	12 mm for Camera about 10 cm above umbilicus, two 8 mm in right and 8 mm in left upper and 12 mm in left lower abdomen
Uterine manipulator	Reusable	Disposable
Hysterectomy and BSO	Securing and dividing uterine vessels laparoscopically while ligating and dividing parametria vaginally	Uterus totally freed laparoscopically, and then removed via vagina
Closing vagina	Vaginal	Laparoscopic
Local cervical anesthesia	At onset of vaginal phase; levobupivacaine 0.5% 20 mL or lidocaine with adrenaline 0.25% 20 mL	At onset of operation; Chirocaine 0.5% 20 mL or lidocaine with adrenaline 0.25% 20 mL

BSO, bilateral salpingo-oophorectomy.
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<.05 were considered to be statistically significant.

Results

All but 3 patients were operated on according to the randomization plan (Figure 1). Two patients were diverted to a laparotomy because of anesthesiologic reasons, and were excluded from the analysis. One patient randomized to the traditional group was however operated on with the aid of the robot, chosen by a consultant outside the study team. This patient is included in the traditional group in the intention-to-treat analysis. The treatment arms were well balanced in relation to all factors studied (Tables 2 and 3). The median operation time in the traditional laparoscopy group (n = 49) was 170 (range 126-259) minutes, while it was 139 (range 86-197) minutes in the robotic surgery group (n = 50). The difference (18%) is statistically significant ($P < .001$) (Figure 2 and Table 4). The corresponding mean operation times were 178 (SD 32) vs 141 (SD 26) minutes ($P < .001$), respectively.

There were 5 vs 0 conversions to laparotomy in the traditional laparoscopy and robotic surgery groups, respectively ($P = .027$). The reasons for these conversions included adhesions in 2 cases, and disseminated cancer, bleeding from the abdominal wall (trocar site), and a uterus too large to be removed through the vagina, 1 case each. The conversions did not extend operation times: excluding the cases with conversions, the operation times were median 171 (range 126-250) and mean 176 (SD 29) minutes (n = 44). The difference as compared to the robotic group is significant also in this setting ($P = .001$).

In addition to the operation time, the total time spent in the operation room was shorter in the robotic surgery group (Table 4) The median docking and robotic console times were 6 (range 1-16) and 106 (range 59-164) minutes, respectively. In both groups the operation times were significantly longer for obese patients. For 51 patients, whose BMI was <30, the operation times were median 144 (range 86-227) and mean 148 (SD 31) minutes, respectively. The corresponding figures for obese (BMI

TABLE 2
Demographic data and medical history

	Traditional, n = 49	Robot, n = 50	*P*
Age, y, median (range)	70 (48–83)	67 (43–84)	.298
BMI, kg/m^2, median (range)	29 (20–45)	29 (20–46)	.787
Parity, n, median (range)	2 (0–4)	2 (0–9)	.971
Preoperative hemoglobin, g/L, median (range)	135 (88–160)	136 (109–159)	.782
Disease, n (%)			
Cardiovascular	27 (53)	33 (66)	.181
Pulmonary	4 (8)	6 (12)	.741
Diabetes	9 (18)	4 (8)	.127
Thromboembolic	3 (6)	3 (6)	1.000
Other	20 (39)	24 (49)	.373
Existing antithrombotic medication, n (%)	7 (14)	7 (14)	.967
Previous abdominal surgery,[a] n (%)	28 (57)	24 (48)	.362

BMI, body mass index.
[a] Majority of operations were laparotomies, 92% in both groups.
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TABLE 3
Histopathological findings and postoperative adjuvant therapy

	Traditional, n = 49	Robot, n = 50	*P*
Size of uterus, g, median (IQR; range)	87 (70–116; 54–460)	97.5 (80–125; 55–286)	.160
Lymph node count, median (range)	23 (11–50)	25 (14–52)	.273
Iliac area, median (range)	11 (4–28)	10.5 (3–31)	.481
Obturator area, median (range)	12 (1–29)	14.5 (5–30)	.137
Stage, n (%)			.437
IA	32 (65)	31 (65)	
IB	9 (18)	12 (25)	
II	3 (6)	0 (0)	
III–IV	5 (10)	5 (10)	
Grade, n (%)			.324
1	31 (63)	34 (68)	
2	14 (29)	10 (20)	
3	0 (0)	3 (6)	
Other	4 (8)	3 (6)	
Adjuvant therapy, n (%)	19 (39)	22 (44)	.598
Chemotherapy	5 (10)	5 (10)	
External radiation	6 (12)	3 (6)	
Chemotherapy and external radiation	3 (6)	5 (10)	
Brachytherapy	4 (8)	9 (18)	
Hormonal therapy	1 (2)	0 (0)	

IQR, interquartile range.

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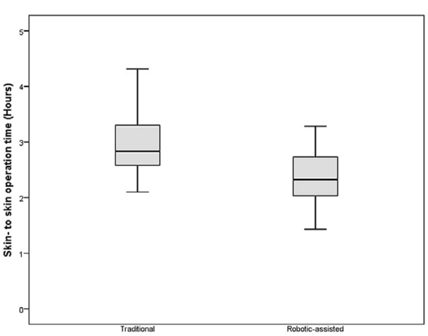
>30, n = 48) patients were 168 (range 104-259) and 171 (SD 33) minutes. The difference is statistically significant at $P = .001$. Interestingly, the time benefit by robotic surgery for obese patients, albeit significant at $P = .001$, was smaller (median 30 minutes) than for normal-weight patients (median 41 minutes) ($P < .001$).

FIGURE 2
Operation skin-to-skin times



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The groups did not differ in the number of lymph nodes harvested (Table 3). Lymph node metastases were found in 1 patient in the traditional laparoscopy group and in 2 patients in the robotic surgery group. In both groups, lymphadenectomy was omitted in 2 cases, due to a disseminated disease for all 4 patients. The lymph node yield was greater in obese women: the median number of nodes was 21 (range 13-47) and 27.5 (range 11-51) in patients with a BMI <30 or >30, respectively ($P = .001$).

In the final histopathological report vs the preoperative biopsy, the diagnosis was changed for 10 patients. In the traditional laparoscopy group, 1 endometrioid adenocarcinoma was changed to carcinosarcoma and 3 endometrioid adenocarcinomas to mixed cell endometrial carcinomas, respectively. In the robotic surgery group, 3 low-grade endometrioid carcinomas were upgraded to high-grade endometrioid carcinomas, 1 tumor changed to a mixed-cell carcinoma, and finally, 2 endometrioid carcinomas changed to extrauterine carcinomas (1 tubal and 1 ovarian carcinoma).

The treatment arms did not differ from each other in respect to the amount of bleeding and the length of postoperative hospital stay (Table 4). However, obese women bled more than normal-weight women. The median volume of bleeding was 50 (range 5-400) vs 100 (range 20-1200) mL in women with a BMI <30 or >30, respectively ($P = .017$).

A total of 12 (24%) of the traditional laparoscopy patients and 18 (36%) of the robotic-assisted laparoscopy patients had complications (including intraoperative and all postoperative complications), respectively ($P = .275$) (Table 5). All 4 intraoperative complications occurred in the traditional laparoscopy group. One patient whose operation was converted to a laparotomy bled 1100 mL during laparotomy. Other surgical complications included a bladder injury and 1 case of intestinal thermal damage. Both were repaired laparoscopically. One patient had reversible carbon-dioxide retention that required a break in the operation.

No postoperative deaths occurred during the study period, nor were any thromboembolic complications encountered. The total number of postoperative complications was higher, albeit not significantly, in the robotic surgery group (18 vs 10, $P = .085$) (Table 5). Five (10%) and 11 (22%) patients had major early and late postoperative complications in the traditional laparoscopy and robotic surgery groups, respectively ($P = .111$). In the robotic surgery group, 11 patients had 12 major complications, of which 4 were related to bleeding. One of the patients needed an embolization of the internal

TABLE 4
Operative outcomes

	Traditional, n = 49	Robot, n = 50	*P*
Operation time, h:min, median (range)	2:50 (2:06—4:19)	2:19 (1:26—3:17)	<.001
Operating room time, h:min, median (range)	3:48 (2:51—5:36)	3:17 (2:27—4:22)	<.001
Bleeding, mL, median (IQR; range)	50 (50—125; 20—1200)	50 (50—113; 5—500)	.504
Conversions, n (%)	5 (10)	0 (0)	.027
1-d Postoperative hemoglobin, median (range)	123 (90—145)	118 (83—145)	.298
Decrease in hemoglobin, g/L, median (%)	15 (—10 to 44) n = 42	15 (2—65) n = 48	.656
Blood transfusion, (n) (%)	2 (4)	6 (12)	.269
1-d Postoperative VAS, median (range)	2.5 (0—7) n = 35	3 (0—7) n = 42	1.000
2-d Postoperative VAS, median (range)	2 (0—6) n = 14	2 (0—6) n = 13	.430
Hospital stay, d, median (IQR; range)	2 (1—2; 1—7)	1 (1—2;1—4)	.215

IQR, interquartile range; *VAS*, visual analog scale for pain (1—10).
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iliac artery in addition to transfusion. In the whole study population, only 1 patient in the robotic surgery group needed a reoperation. One month after the primary operation, she developed a rectovaginal fistula that required a temporary loop transversostomy, with full recovery. A nerve injury, located by electroneuromyography in the nerve of the left iliopsoas muscle, caused partly reversible pain and numbness of the left foot. Two patients in both groups developed an abscess, which required drainage procedures for both of the patients in the traditional laparoscopy group and for 1 patient in the robotic surgery group.

Comment

Several retrospective studies have implied that the operation time is longer in robotic-assisted than in traditional laparoscopic operations for endometrial cancer.[11-15] We were not able to find previous randomized controlled trials on the use of robotic-assisted surgery for endometrial cancer, but the same tendency was seen in 2 of the randomized hysterectomy trials for benign indications we found.[16,17] However, in the study of Lönnerfors et al,[18] comparing robotic-assisted hysterectomy to vaginal or traditional laparoscopic hysterectomy, the median operative times did not differ between the groups. The aim of this randomized, controlled prospective study was to show that robotic surgery does not take markedly longer to perform than traditional surgery. We set the limit of a "marked" lengthening to a 25% increase in operation time. Actually, robotic-assisted surgery turned out to be 18% less time-consuming than traditional surgery. In fact, there are some retrospective studies pointing at the same direction.[19-21]

Another general impression has been that in any case the total time spent in the operation room is longer for robotic-assisted than for traditional surgery, as the preparation takes longer. Even this impression turned out to be wrong: the total time spent in the operation room was shorter in the robotic surgery group, because the preparation time was in fact identical for both groups. However, one has to take into account that the operative team's learning curve was already stabilized by the time the study was initiated, and the same surgeons, anesthesiologists, and nurses had already worked as a team in >100 robotic operations by the time the trial was begun. In our earlier study, we showed that the preparation and docking times get progressively shorter as the team gains experience.[8] It should however be noted that our hospital is very experienced also with traditional laparoscopy, which has been used for endometrial cancer since 1990s.[22]

We expected the advantages of the robotic-assisted technique to become especially evident with obese patients. However, actually the time saved by robotic-assisted technique was more evident in normal-weight than in obese patients (41 vs 30 minutes, respectively). In previous studies addressing obesity and laparoscopic operations, the number of conversions has been lower in robotic-assisted surgery than in traditional laparoscopic surgery.[19,23] In the present study, all conversions had to be performed in the traditional laparoscopy group, and 4 of 5 conversions were performed on obese patients. It is of course possible that the lack of conversions in the robotic group is by chance only, and in the report of our initial experience with robotic-assisted surgery the conversion rate was in fact 4%.[8] Those conversions took place in the beginning of our learning curve with robotic-assisted surgery, and similarly in the report by Paley et al,[24] where they described their first 1000 robotic-assisted operations, the conversion rate was 2.9%. However, our learning curve was already well established, when this randomized trial was started, and in fact, a low rate of conversions has been

TABLE 5
Complications

	Traditional, n = 49	Robot, n = 50	*P*
Complications			
All complications, n (%)	12 (24)	18 (36)	.275
Intraoperative, n (%)	4 (8)	0 (0)	.056
Vascular injury/bleeding	1	0	
Bladder injury	1	0	
Intestine injury	1	0	
Respiratory insufficiency	1	0	
All postoperative, n (%)	10 (20)	18 (36)	.085
Major early, n (%)	1 (2)	5 (10)	.204
Intraabdominal bleeding	1	4	
Nerve injury	0	1	
Minor early, n (%)	3 (6)	4 (8)	1.000
Wound bleeding	1	3	
Nerve injury	0	1	
Urine retention	2	0	
Major late, n (%)	4 (8)	7 (14)	.525
Infection	4	6	
Rectovaginal fistula	0	1	
Minor late, n (%)	2 (4)	5 (10)	.436
Wound infection	1	3	
Urinary tract infection	1	1	
Foot swelling	0	1	

One patient may have >1 complication.
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evident in other studies. In the study of Cardenas-Goicoechea et al[25] with 102 robotic-assisted and 173 traditional laparoscopic operations, there were only 1 vs 9 conversions, respectively.[13] Also in their later report the rate of conversions in robotic-assisted staging operations was very low or 0.5%.[25]

The lymph node yield was not better in the robotic surgery group than in the traditional laparoscopy group. One explanation to this may be that, in our hospital, as stated above, there is a long tradition of laparoscopic surgery for endometrial cancer,[22] which suggests that the laparoscopic technique was fully adopted by the time robotic assistance was introduced in our hospital in the beginning of the year 2009. On the other hand, according to the review by Gaia et al,[26] the number of pelvic lymph nodes harvested is comparable between traditional and robotic-assisted laparoscopic surgery. In both of our treatment groups, the lymph node yield (median 23 and 25 in the traditional laparoscopy and robotic surgery groups, respectively) favors well with previous studies (17.8 vs 18.5, in the review of Gaia et al[26] in 2010). Although the rate of postoperative complications was somewhat greater in the robotic surgery group, this was counterbalanced by the fact that intraoperative complications occurred and conversions had to be performed only in the traditional laparoscopy group. As a whole, both techniques turned out to be effective and safe alternatives for the operative treatment of endometrial cancer. Apart from the above-mentioned rectovaginal fistula, no significant late adverse events like hernias emerged during the follow-up. This is in agreement with previous studies, as the meta-analyses by Reza et al[27] and Wright et al[28] found similar and low[25] morbidity rates for these 2 techniques. Also according to a recent study comparing robotic-assisted surgery to laparotomy for endometrial cancer, hernia formation was a problem only in the laparotomy group.[29]

The strengths of this study are the prospective randomized and controlled setting, and therefore a well-balanced and unbiased distribution of the patients into the groups. In addition, the learning curves of the surgeons and the whole team did not affect the results. The rather limited number of patients may be considered as a weakness. However, large randomized controlled trials in surgery are quite challenging to carry out; even in this trial it took 3 years to recruit the patients. However, the sample size was sufficient to perceive significant differences between the groups. Another shortcoming is that nowadays PLND is quite seldom carried out alone, without a simultaneous paraaortic lymphadenectomy.

In this randomized controlled trial we showed that contrary to previous assumptions, at least in our hands, hysterectomy, BSO, and PLND are faster to perform using robotic-assisted technique as compared to traditional laparoscopy. Hence, robotic surgery offers an effective and safe alternative in the surgical treatment of endometrial cancer. ■

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Author and article information

From the Department of Gynecology and Obstetrics, Tampere University Hospital (Drs M. Mäenpää, Nieminen, Tomás, and J. Mäenpää); School of Medicine (Dr J. Mäenpää) and School of Health Sciences (Ms Luukkaala), University of Tampere; and Department of Pathology, Fimlab Laboratories (Dr Laurila) and Science Center (Ms Luukkaala), Pirkanmaa Hospital District; Tampere, Finland.

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Corresponding author: Minna M. Mäenpää, MD. minna.maenpaa@pshp.fi

Costs of Robotic-Assisted Versus Traditional Laparoscopy in Endometrial Cancer

Riikka-Liisa K. Vuorinen, MD, Minna M. Mäenpää, MD,* Kari Nieminen, PhD,* Eija I. Tomás, PhD,* Tiina H. Luukkaala, MSc,†‡ Anssi Auvinen, PhD,§ and Johanna U. Mäenpää, PhD*‡*

Objectives: The purpose of this study was to compare the costs of traditional laparoscopy and robotic-assisted laparoscopy in the treatment of endometrial cancer.
Methods and Materials: A total of 101 patients with endometrial cancer were randomized to the study and operated on starting from 2010 until 2013, at the Department of Obstetrics and Gynecology of Tampere University Hospital, Tampere, Finland. Costs were calculated based on internal accounting, hospital database, and purchase prices and were compared using intention-to-treat analysis. Main outcome measures were item costs and total costs related to the operation, including a 6-month postoperative follow-up.
Results: The total costs including late complications were 2160 € higher in the robotic group (median for traditional 5823 €, vs robot median 7983 €, $P < 0.001$). The difference was due to higher costs for instruments and equipment as well as to more expensive operating room and postanesthesia care unit time. Traditional laparoscopy involved higher costs for operation personnel, general costs, medication used in the operation, and surgeon, although these costs were not substantial. There was no significant difference in in-patient stay, laboratory, radiology, blood products, or costs related to complications.
Conclusions: According to this study, robotic-assisted laparoscopy is 37% more expensive than traditional laparoscopy in the treatment of endometrial cancer. The cost difference is mainly explained by amortization of the robot and its instrumentation.

Key Words: Robotic-assisted surgery, Endometrial cancer, Cost analysis, Gynecologic oncology

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Endometrial cancer is the most common gynecologic malignancy in the developed countries with 167,900 estimated new cases and 34,700 estimated deaths in 2012.[1] Primary treatment of endometrial cancer is hysterectomy and bilateral salpingo-oophorectomy, commonly accompanied by pelvic or pelvic and para-aortic lymphadenectomy (PALND).[2] Surgical methods for treating endometrial cancer include laparotomy, traditional laparoscopy, and robotic-assisted laparoscopy. According to cost-effectiveness analysis by Leitao et al,[3] laparotomy was the most expensive approach compared with

*Department of Obstetrics and Gynecology, Tampere University Hospital; †Science Centre, Pirkanmaa Hospital District; ‡Faculty of Medicine and Life Sciences, University of Tampere; §Faculty of Social Sciences, University of Tampere, Tampere, Finland.
Address correspondence and reprint requests to Riikka-Liisa Vuorinen, MD, Department of Obstetrics and Gynecology, Tampere University Hospital, PO Box 2000, FI-33521, Tampere, Finland. E-mail: riikka.vuorinen@pshp.fi.

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traditional laparoscopy and robotic-assisted laparoscopy (total costs without equipment: USD 24,433, USD 20,289, and USD 20,467, respectively). The robot platform has been in use at Tampere University Hospital since 2009, and the robot is used by urologists, gynecologists, and thoracic surgeons, with an annual rate of 345 to 400 operations.

The aim of this analysis was to compare the costs of conventional laparoscopy and robotic-assisted laparoscopy in the treatment of endometrial cancer, to evaluate possible differences and identify factors influencing the costs within a randomized trial.

MATERIALS AND METHODS

In a clinical trial, 101 patients presenting with endometrial cancer were randomized into 2 arms, traditional laparoscopy (traditional, n = 51) and robotic-assisted laparoscopy (robot, n = 50). Inclusion criteria were a low-grade (Grade 1–2) endometrial cancer, a scheduled staging operation, and a signed informed consent. Exclusion criteria included a narrow vagina or a uterus too large to be removed through the vagina and ineligibility for a deep Trendelenburg position. The details of the study population, randomization procedure, and operations have been described in detail previously.[4]

The operations were performed at a tertiary referral center, the Department of Obstetrics and Gynecology of Tampere University Hospital, Tampere, Finland from 2010 to 2013 by gynecologic oncologists with several years of experience with laparoscopic surgery. The study protocol was approved by the Research Ethics Committee of Tampere University Hospital (identification code ETL R10081) and is registered at www.clinicaltrials.gov (NCT 01466777).

TABLE 1. Variable definitions

Variables	Both Groups	Traditional	Robot	Comment
Instruments	Disposable instruments and materials, maintenance costs for reusable instruments, and OR supplies hemostatic matrix if used	Energy instrument costs	Instrument cost per operation (4 basic instruments)	
In-patient stay	Room and board, ward personnel, and ward basic medication			
Laboratory	Based on the needed studies during operation and in-patient stay			
Radiology	Based on the needed imaging studies during operation and in-patient stay			
Blood products	Blood transfusions and laboratory samples related to preparation or transfusions			
Operation personnel	0.5 anesthesiologist and 3.25 OR nurses for each operation			Related to OR time
Equipment and OR	Costs of running the OR and the fixed equipment	Amortization of a basic laparoscopy tower	Amortization of the robot console	Related to OR time
General costs	Administrative costs, costs that cannot be calculated elsewhere			Related to OR time
Operation medication	Anesthesia costs and local anesthetics			Related to OR time
Surgeon costs	2 operating specialists			Related to operation time
PACU costs	0.3 nurses per patient and facilities			Related to PACU time
Complications	Additional clinical visits, readmissions, and radiology			

OR=operating room
PACU=post-anesthesia care unit

The costs were calculated retrospectively in euros. The cost variables are presented in Table 1.

The patient data were collected from the operation and onwards over the subsequent follow-up period of 6 months. All contacts and procedures at follow-up hospitals (imaging studies, readmissions, operative treatment) were recorded. These contacts and the costs related to them were calculated in complications and are referred in this article also as late complications. In complication costs, all expenses related to the contact have been taken into account. This includes also all out-patient visits, which led or did not lead to any procedures. Patients contacted clinics for various reasons such as swelling, bruises, and vaginal bleeding among other complaints. Most of these were normal postoperative symptoms. Because of swelling in lower extremities, many patients underwent a Doppler ultrasound imaging to exclude deep venous thrombosis with no findings.[4]

Public health care in Finland uses an internal accounting and billing system within the hospitals. Different hospital units offer services based on their expertise such as anesthetic services, operating room (OR) services, laboratory services, and consultations provided by other specialties like urologic surgery. We searched the hospital databases to retrieve the actual costs of each operation.

The original expense data from 2012 was used as the basis for calculating costs for operation personnel, amortization of the laparoscopy towers and the robot console, OR costs, medication during the operation, and general costs related to the hospital infrastructure. The 2012 expense data was chosen because it represents the midpoint of the study period.

The amortization and use of an energy instrument in traditional laparoscopy group was also included in the instrument costs; an energy instrument was used in 15 operations, based on the operating surgeon's judgment.

Costs related to the instrumentation, in-patient stay, radiology, and laboratory services as well as blood products were calculated or retrieved from the database according to the actual time (exact date or at least year) of the operation. In-patient stay, radiology, laboratory, and blood product expenses were retrieved from the internal accounting system. For disposable instruments and products, we used the real hospital purchase costs, according to the reported data on each operation, and we included in every operation a basic array of instruments and equipment involved in the operative set-up. Traditional and robotic operations had a different basic package based on the needs of the operative method. For reusable instruments, the maintenance costs were calculated. For robot instruments, the cost of amortizing (maximum 10 operations per instrument), and the maintenance costs were taken into account.

The robot at Tampere University Hospital is the Da Vinci S surgical system (Intuitive Surgical, Inc, Sunnyvale, Calif). It is a leased product with a 10-year contract. The annual leasing and maintenance costs are 196,000 € and 140,000 €, respectively. We divided these costs with the total number of operations during the year 2012 to calculate the robot platform amortization cost per robot operation.

One patient was originally randomized into the traditional laparoscopy group, but the surgeon decided to change the operative procedure to robotic-assisted laparoscopy because of the obesity of the patient. Because of this randomization violation, secondary analyses were performed besides the primary intention-to-treat analysis, which is a per protocol analysis with groups based on the actual operative manner (this patient was included in the robot arm), and also excluding this patient.

Two patients from the traditional laparoscopy group who were not suitable for laparoscopic operation were operated through laparotomy, and their data was not analyzed in the study.[4] Consequently, the final number of patients in the analysis was 49 in the traditional group and 50 in the robotic-assisted group.

Distributions of cost factors were shown by medians with interquartile ranges due to the skewed distributions and outliers. Differences between traditional and robotic-assisted laparoscopic surgical costs were analyzed by nonparametric independent-samples Mann-Whitney *U* test. Categorical variables were tested by Pearson χ^2 test or by Fisher exact test if the expected values were too small. Statistical analyses were performed by IBM SPSS Statistics version 23 (IBM Corp, Armonk, NY). *P* values less than 0.05 were considered statistically significant.

RESULTS

Because there were no substantial differences in the results of the intention-to-treat and treatment received analyses, only the results of the intention-to-treat analysis are presented here. Results using the secondary analyses are given in the Supplemental Tables (S1 to S4 http://links.lww.com/IGC/A545).

The item costs were higher in the robotic-assisted laparoscopy arm for instruments, equipment, and OR, as well as postanesthesia care unit (PACU) (Table 2). Traditional laparoscopy had higher costs for operation personnel and medication, general costs and surgeon costs, but these differences were relatively small (Table 1 for variable definitions, Table 2). There were no significant differences in costs related to in-patient stay, laboratory and radiology services, or blood products. The median total costs for the robotic-assisted laparoscopy, including late complications were 2160 € higher than for traditional laparoscopy (1.4-fold, cost per operation: 7982 € vs 5823 €, respectively; Fig. 1).

There were 5 conversions to laparotomy in the traditional laparoscopy group and none in the robot group.[4] The total costs without late complications for these patients were substantially higher than for the rest of the traditional laparoscopy patients (nonconversions Md 5352 € vs conversions 7149 €, $P < 0.001$) There was also a significant difference in the length of in-patient stay (Md 1 vs 4 days, P <0.001), which increased the costs of the in-patient stay (1114 € vs 2148 €, $P = 0.002$). Moreover, there was a significant difference in PACU time (Md 2 hours and 22 minutes vs 3 hours 33 minutes, $P < 0.001$), which also affected the PACU costs (704 € vs 938 €, $P < 0.001$). The median total costs related to the laparoscopy-laparotomy converted operations are close to the median total cost of the robot arm without complications (7415 €).

Ten patients in the traditional group and 20 patients in the robot group contacted the follow-up hospitals or had

TABLE 2. Itemized median costs for traditional vs robot-assisted laparoscopy for endometrial carcinoma, intention-to-treat analysis within the Tampere randomized trial, and cost factors

	Traditional (n = 49)			Robot (n = 50)			Difference	
Variables	**Md €**	**(IQR €)**	**%**	**Md €**	**(IQR €)**	**%**	**€**	***P***
Instruments	214	(171–421)	5.9	1813	(1798–1817)	23.9	−1599	<0.001
In-patient stay	1387	(1002–1635)	25.2	1092	(932–1422)	15.8	295	0.130
Laboratory	824	(457–918)	13.3	791	(526–909)	9.3	33	0.845
Radiology	0	(0–37)	0.6	0	(0–0)	1.1	0	0.321
Blood products	18	(17–35)	0.6	18	(0–40)	0.6	0	0.674
Operation personnel*	844	(797–995)	16.2	729	(661–833)	9.7	115	<0.001
Equipment and OR	232	(217–295)	4.7	1172	(1064–1340)	15.7	−940	<0.001
General costs	78	(73–91)	1.5	67	(61–77)	0.9	11	<0.001
Operation medication	91	(86–108)	1.8	79	(72–90)	1.1	12	<0.001
Surgeon costs	896	(806–1,049)	17.0	735	(643–866)	9.8	161	<0.001
PACU costs	704	(704–938)	13.3	938	(704–938)	12.1	−234	<0.001
Total costs without late complications	5487	(4766–6184)		7415	(6937–8057)		−1928	<0.001
Complications	766	(349–1532)		844	(421–2883)		−78	0.530
Total costs with complications	5823	(4912–6243)		7983	(7236–8400)		−2160	<0.001

Md = median value.
IQR = interquartile range.
*Nurses and an anesthesiologist.

complications reported. The related median costs were 766 € and 844 € per patient, respectively (P = 0.530).

The operative time as well as the OR time were significantly shorter in the robot group, whereas PACU time was shorter in the traditional group (Table 3).[4]

Although there was no significant difference in the median length of postoperative in-patient stay (Table 3), 1 patient in the traditional group was not discharged until postoperative day 7. Physically, the patient's recovery from the surgery did not differ from that of other patients, but the patient's mental status did not allow discharge, and she was waiting for a transfer to a municipal hospital. This created an outlier in the in-patient stay costs (3343 €). We were unable to calculate the costs of the following municipal hospital stay.

One patient in the robot group underwent embolization while she was in the PACU because of a bleeding complication. This patient stayed in the PACU for 16 hours and 2 minutes causing an outlier in the PACU time and PACU costs (4492 €), as well as the embolization cost in the Radiology Department (2884 €). We included the costs (embolization, laboratory, radiology, PACU) in this patient's primary operation period, not itemizing them stratified according to the complications,

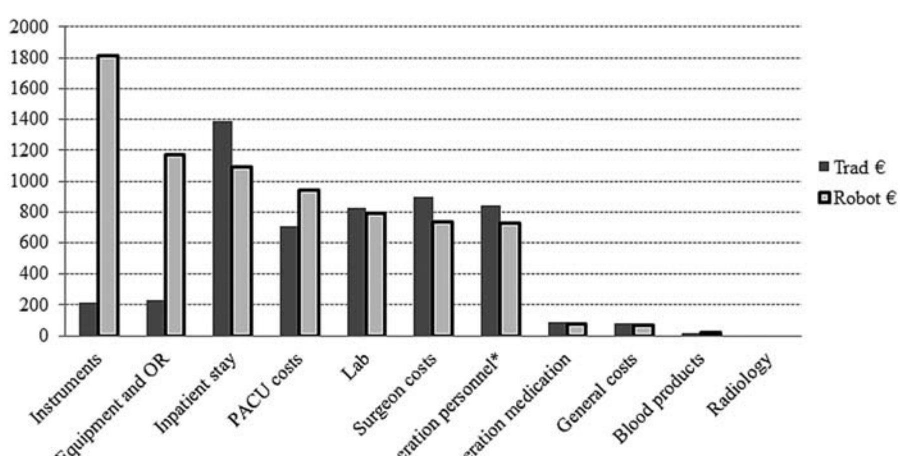

FIGURE 1. Cost variables, comparison (accompanying.tif-file). Median values (€). *Nurses and anesthesiologist.

TABLE 3. Time-related items in traditional vs robot-assisted laparoscopy for endometrial carcinoma in the Tampere randomized trial, intention-to-treat analysis

	Traditional (n = 49)		Robot (n = 50)		
Variables	**Md**	**(IQR)**	**Md**	**(IQR)**	***P***
Sick leave, d	27.5 (n = 12)	(24–33)	28 (n = 13)	(25–29.5)	0.728
OR time	3:48	(3:35–4:29)	3:17	(2:59–3:45)	<0.001
Operation time	2:50	(2:33–3:19)	2:19	(2:02–2:44)	<0.001
PACU time	2:36	(2:03–3:08)	3:05	(2:38–3:31)	0.001
Discharge, d	2	(1–2)	1	(1–2)	0.215

Md = median value.
IQR = interquartile range.

because it was difficult to reliably differentiate the costs of this complication from the costs of the surgery itself, for example, in the PACU costs.

One patient in the robot group needed 2 reoperations because of a rectovaginal-fistula. This patient also had repeated imaging studies and readmissions because of the complication. These costs created an outlier in complication costs (14,818 €).

No postoperative deaths occurred during the study period nor were there any thromboembolic events during the follow-up.[4]

There was no significant difference between the 2 arms in duration of sick leave (Table 3). Most of the patients did not receive sick leave because they were already retired. Consequently, sick leave costs were not calculated in this analysis.

Robot instrument cost per operation was 1030 € (including 4 basic instruments used in the operations), and the amortization cost of the robot console per operation was 939 € according to the 2012 expense data (taken into account in equipment and OR costs). On this basis, we calculated costs per duration of OR time–related amortization cost (5.95 € per minute) and applied it individually for each operation in accordance with the operating time. Therefore, the equipment and OR costs for some patients can be less than 939 € (range, 844 €–1503 €).

CONCLUSIONS

The median actual costs of the robotic-assisted laparoscopy were 1928 € (35%) higher per patient than the costs related to traditional laparoscopy. Although direct international comparisons are difficult to make because of differences in national health care funding systems, our results seem to be comparable with findings in previous studies, showing robotic-assisted laparoscopy to be 17% to 33% more expensive.[5,6] Amortization of the robot console and costs involved with robot instrumentation are the major determinants of the incremental costs related to robotic-assisted surgery.[5–9] Amortization can be minimized by increasing the number of operations. However, because a set of robot instruments can only be used in 10 operations, the instrument costs are practically fixed. Although we have previously shown that the operation time is shorter in robotic-assisted than traditional laparoscopic operations,[4] the shorter operation time was not enough to balance out the costs of amortization of the robot console and the use of robot instruments.

In Finland, doctors and surgeons in the public health care receive a monthly salary instead of fee for service. This explains the lower labor cost of surgeon per operation compared with a previous US study.[3] In our study, the surgeon cost is related only to the duration of the operation.

The major strength of this study is the randomized design, ensuring an unbiased comparison between the treatment arms. The learning curve effect was also minimized as robotic surgery for gynecologic indications was started at our hospital already in March 2009. We have previously shown that the learning curve for robotic surgery is relatively short or 10 operations.[10] Moreover, our experience with laparoscopic surgery for endometrial cancer dates from 1990s.[11] Both operative techniques were therefore already well-established at the time the randomized trial was initiated.

The 2 groups were well balanced in relation to all major patient characters.[4]

The costs were calculated in a detailed fashion for each operation based on actual cost items, including even from the surgeons' gloves and threads used.

During the time of the study design, the standard surgical treatment of endometrial cancer at our institution was hysterectomy, bilateral salpingo-oophorectomy, and in most cases, pelvic lymphadenectomy (PLND). These 3 procedures were scheduled to be performed to all of the randomized patients. However, PLND was not performed on 2 patients in both arms (total n = 4) because of a disseminated disease.[4]

The costs of PALND were not evaluated. Current guidelines encourage PALND, besides PLND, to be performed in patients with high-risk endometrial cancer, whereas in the case of low-risk cancer, only hysterectomy and bilateral salpingo-oophorectomy without LND should be performed.[12] Because extending the lymphadenectomy to the para-aortic area makes traditional laparoscopy challenging to perform the cost difference might have been smaller if PALND were included in the randomized study design.[13]

Although the number of patients was rather limited, the outliers encountered in some variables did not substantially affect the final results.

There are some local factors that inevitably constrain the generalizability of the results. Our robot console and its PACU are located in a separate building apart from the Department of Obstetrics and Gynecology and its ORs. This increases the expenses because of additional PACU time.

Quality of life was not investigated in this study, which can be considered a limitation.

Laparoscopic approach has replaced laparotomy in the operative treatment for endometrial cancer.[12] At present, laparotomy should not be considered as the primary operation method anymore now that minimally invasive methods have been evolved.[13,14] Moreover, according to a recent study comparing the costs of robotic-assisted laparoscopic hysterectomy to open hysterectomy, laparotomy was more expensive, mainly because of longer in-patient stay.[15] In the field of laparoscopy, the robotic-assisted technique has introduced many advantages such as diminished blood loss, wristed instruments, 3-dimensional stereoscopic vision, better ergonomics for surgeon, and a shorter learning curve.[9–11,16,17] This was reflected also in the present study, where no conversions to laparotomy had to be undertaken in the robot group as opposed to 5 conversions in the traditional group. The total costs of the converted operations were almost as high as the costs of the robotic-assisted operations (Md 7149 € vs 7415 €, respectively).

In contrast to clinical operations performed for real patients, in which setting each robotic instrument can be used only 10 times, in the preclinical training phase, the same instruments can be used 30 times (data obtained during from robotic training at Tampere University Hospital, Da Vinci S surgical system; Intuitive Surgical, Inc, Sunnyvale, Calif). If robotic instruments could also clinically be used 30 times, it would decrease the instrument costs by 688 €. On the other hand, if the annual number of gynecological operations at our institution would be increased from 84 to 120, with 3 instead of 2 daily operation, the amortization costs would decrease by 282 € per operation. By such means, the median total costs for robotic surgery would be 6445 €, and the difference between the 2 operation types would decrease to 17%.

We were unable to assess patient outcomes in terms of quality-adjusted life year (QALY) (because no obvious difference in complications or other patient outcomes were found), so real cost-effectiveness analysis was not possible. However, applying a cost-effectiveness threshold of 50,000 €; per QALY to the observed cost difference of 2160 € per operation, it would mean that 1 QALY would need to be gained per 26 patients operated to reach the threshold.

The robotic-assisted technique in the staging of endometrial carcinoma (hysterectomy, bilateral salpingo-oophorectomy, and PLND) increases the total treatment costs by one third compared with the traditional technique. In our setting, this translates into roughly 2000 € per patient. For further research, it would be beneficial to calculate the costs in similar form including the PALND.

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