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ONCOLOGIC AND FUNCTIONAL OUTCOMES AFTER ROBOT - ASSISTED RADICAL HYSTERECTOMY FOR CERVICAL CANCER

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Oncologic and functional outcomes after robot-assisted radical hysterectomy for cervical cancer

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To Martinho, Hugo, Theo and Gabriella

ABSTRACT

Background: Cervical cancer is the fourth most common cancer in women worldwide, but the incidence has rapidly declined in developed countries after the introduction of structured screening programs. This disease is caused by persistent HPV infection commonly acquired in adolescence, thereby affecting young women. In countries with established screening programs, early detection has resulted in favorable prognosis. Surgical treatment is the main treatment for early-stage disease and radical hysterectomy (RH) cures more than 90% of those afflicted. However, this treatment is associated with considerable morbidity and impaired quality of life (QoL). In 2005, robot-assisted laparoscopic radical hysterectomy (RRH), was introduced and subsequently implemented in Sweden. The perceived benefits of minimally invasive surgery (MIS), and of RRH in particular, have not been confirmed. It is therefore imperative to assess the efficacy and safety of this surgical technique, as well as short- and long-term adverse effects, particularly since long-term survival is expected.

Aims: The overall aim was to investigate the oncologic safety of RRH. Secondary aims included assessment of surgical outcomes, health care costs and impact on QoL, bladder, bowel, sexual and lymphatic function after RRH.

Methods: To assess the oncologic and surgical outcomes, two population-based studies were performed (Studies I and II). **Study I** included 304 women who underwent RH stage IA1-IIA during 2006-2015 at Karolinska University Hospital (KUH). Surgical and oncologic outcomes, as well as the costs of RRH and open radical hysterectomy (ORH) were compared. **Study II**, a nationwide cohort study, assessed overall and disease-free survival after RRH and ORH in 864 women with stage IA1-IB1 disease. The functional impact of RRH was investigated in two prospective clinical studies (Studies III and IV) with one-year follow-up. In **Study III**, 26 women undergoing RRH filled in a questionnaire regarding psychological well-being and sexual, bowel, bladder, and lymphatic function. In addition, postoperative ovarian function was measured by change in sex hormones. In **Study IV**, 27 patient-reported outcomes after RRH were assessed using two validated questionnaires concerning bladder function and its impact on QoL. Outcomes were determined objectively by urodynamics and quantification of ablated autonomic nerves.

Results: In the regional study (**Study I**), RRH was associated with an increased risk of recurrence (HR 2.13; 95% CI, 1.06-4.26). The postoperative complication rates (37%) and costs were similar, but the hospital stay was shorter than following ORH. The nationwide study (**Study II**) showed no statistical difference between RRH and ORH with respect to 5-year OS (HR 1.00; 95% CI, 0.50-2.01) and DFS (HR 1.08; 95% CI, 0.66-1.78). Study **III** demonstrated that RRH had a minor effect on sexual function, as well as bowel function. However, bladder impairment and lymphedema remained the main dysfunctions associated with RRH for cervical cancer (**Studies III** and **IV)**. No correlation between the number of autonomous nerves ablated and functional outcomes was observed. In general, postoperative urinary symptoms diminished over time, but persisted in a substantial proportion of the women and may impair QoL.

Conclusions: RRH appears to be safe once surgical proficiency is achieved. Prospective trials are needed to ensure the safety of RRH for cervical cancer. RRH was associated with less perioperative morbidity, and health care costs were similar to those of ORH. RRH seems to have only minor effects on sexual function, though bladder dysfunction remains a significant sequele. The cause of functional impairment after RRH is multifactorial and cannot be explained by nerve ablation alone.

Key words; cervical cancer, radical hysterectomy, robotic, intraoperative complication, hospital costs, recurrence, survival, quality of life, sexual function, bowel function, urinary function, ovarian function, urodynamics

LIST OF SCIENTIFIC PAPERS

I. Emelie Wallin, Angelique Flöter Rådestad, Henrik Falconer

Introduction of robot-assisted radical hysterectomy for early stage cervival cancer: impact on complications, costs and oncologic outcome

Acta Obstet Gynecol Scand. 2017 May;96(5):536-542.

II. Emilia Alfonzo, Emelie Wallin, Linnea Ekdahl, Christian Staf, Angelique Flöter Rådestad, Petur Reynisson, Karin Stålberg, Henrik Falconer, Jan Persson, Pernilla Dahm-Kähler

No survival difference between robotic and open radical hysterectomy for women with early-stage cervical cancer:
results from a nationwide population-based cohort study

Eur J Cancer. 2019 Jul;116:169-177

III. Emelie Wallin, Henrik Falconer, Angelique Flöter Rådestad

Sexual, bladder, bowel and ovarian function 1 year after robot-assisted radical hysterectomy for early-stage cervical cancer

Acta Obstet Gynecol Scand. 2019 Nov;98(11):1404-1412

IV. Emelie Wallin, Henrik Falconer, Joseph Carlson, Lotta Renström Koskela, Angelique Flöter Rådestad

Objective and subjective assessment of bladder function after robot-assisted laparoscopic radical hysterectomy for early stage cervical cancer

In manuscript

CONTENTS

LIST OF ABBREVIATIONS

AMH	Anti-Müllerian hormone
BCI	bladder contractility index
BVE	bladder voiding efficiency
CPP	cost per patient
CD	Clavien Dindo classification
CI	confidence interval
CV	coefficient of variation
DFS	disease-free survival
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
ESGO	The European Society of Gynecological Oncology
FDA	Food and Drug Administration
FIGO	International Federation of Gynecology and Obstetrics
FSFI	The Female Sexual Function Index
FSH	follicle-stimulating hormone
Gy	Gray (SI Unit of absorbed radiation)
HPV	human papilloma virus
HR	hazard ratio
HR-QoL	health related quality of life
KUH	Karolinska University Hospital
LH	gonadotropin luteinizing hormone
LOS	length of stay
LRH	laparoscopic radical hysterectomy
ICIQ-FLUTS	International Consultation on Incontinence Questionnaire Female Lower Urinary Tract Symptoms Modules
ICIQ-LUTSqol	International Consultation on Incontinence Questionnaire Lower Urinary Tract Symptoms Quality of Life Module
LVSI	lymphovascular space invasion
MID	minimal important difference
MIS	minimally invasive surgery
MUCP	maximal urethral closure pressure
NCCN	National Comprehensive Cancer Network
NCR	Swedish National Cancer Registry
ORH	open radical hysterectomy
OS	overall survival
PLND	pelvic lymphadenectomy
PRV	post voidal residual volume
QM	Querleu-Morrow
QoL	quality of life
RCT	randomized controlled trial
RH	radical hysterectomy
RRH	robotic-assisted laparoscopic radical hysterectomy
SEK	swedish crowns
SOE	salpingo-oophorectomy
SLN	sentinel lymph node
SQRGC	Swedish Quality Register of Gynecologic Cancer
SHBG	sex hormone-binding globulin
TNM	Tumor-Node-Metastasis Classifications of Malignant Tumors
USD	US dollars
VAS	visual analogue scale
WHO	The World Health Organization

1 INTRODUCTION

Early stage cervical cancer generally has a favorable prognosis and about half of the women are diagnosed under 50 years of age. Long term survivorship is therefore expected and treatment-induced morbidity and its impact on quality of life (QoL) is of considerable concern. Cervical cancer has traditionally been treated with open radical hysterectomy (ORH), a procedure often associated with major side-effects. Minimally invasive surgery (MIS) techniques by conventional laparoscopy were developed in the early 1990´s and in 2005 treatment of gynecological cancer by robot-assisted surgery was approved by the Food and Drug Administration (FDA). In Sweden traditional ORH for cervical cancer has gradually been replaced by robot-assisted radical hysterectomy (RRH). (*Figure 1*)

To date, few investigations have focused on comparing ORH and MIS with respect to efficacy, safety and survival, as well as impact on QoL. In this context, two major publications in 2018 (1, 2) raised serious concerns about the oncologic safety of minimally invasive radical hysterectomy (RH), including RRH. Since 2019, the National Comprehensive Cancer Network (NCCN), as well as the European Society of Gynecological Oncology (ESGO) recommend RH with an open approach as the gold standard treatment (3, 4).

The four studies in this thesis aimed to investigate the oncological safety (**Studies I** and **II**), as well as surgical outcomes (**Study I**) and functional consequences (**Studies III** and **IV**) after RRH for early-stage cervical cancer.

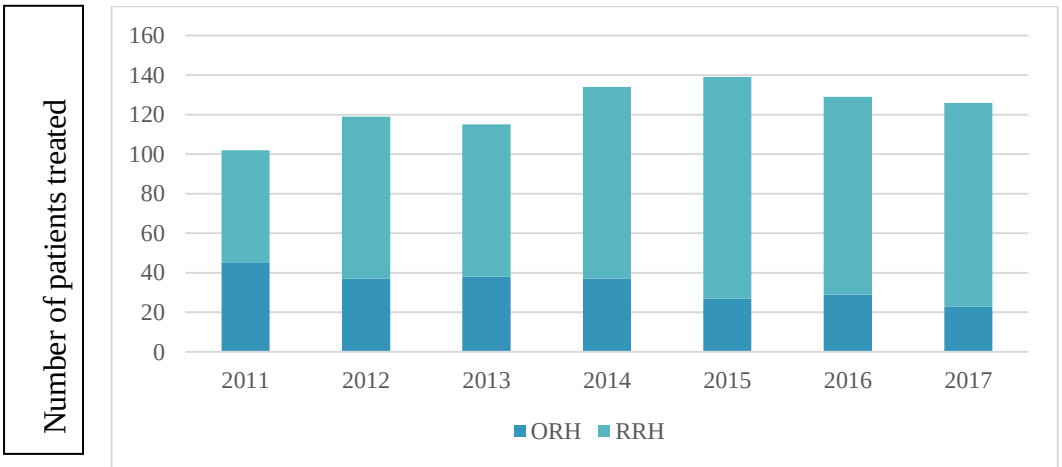


Figure 1. The numbers of open (ORH) and robot-assisted (RRH) radical hysterectomies for early-stage cervical cancer in Sweden 2011-2017.

2 BACKGROUND

2.1 EPIDEMIOLOGY, ETIOLOGY AND PREVENTION

Cervical cancer is the fourth most common cancer worldwide and the most common gynecological cancer, affecting approximately 500,000 women annually (5) (*Figure 2*). In contrast to the high incidence worldwide, the incidence has fallen dramatically in developed countries as a consequence of structured screening programs (6). In Sweden, nearly two-thirds of incident cases occur among women who have not participated in the screening program (7). Early detection has resulted in a generally favorable prognosis, with reported survival ranging between 70-90 % (5, 8, 9). In Sweden the five-year survival rate for stage IB1 is approximately 92% (10).

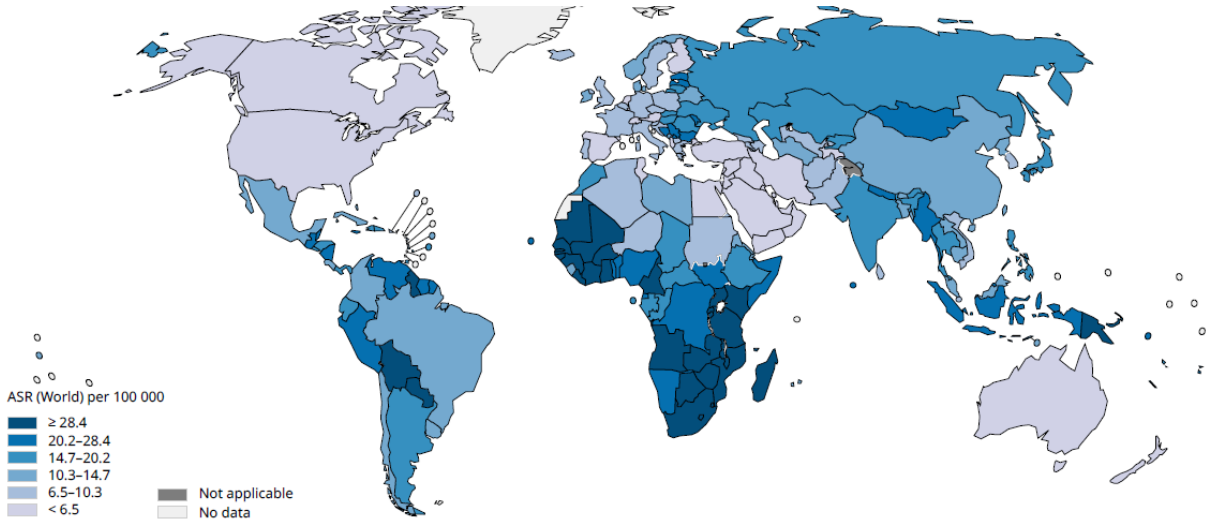


Figure 2. The estimated age-standardized incidence rates of cervical cancer globally in 2018. Data source: GLOBOCAN 2018, Graph production: IARC (http://gco.iarc.fr/today) World Health Organization.

Human papilloma virus (HPV), which is transmitted sexually, is detected in the majority of all cervical cancers and thus considered to be the causal factor (11). The carcinogenic properties of HPV are primarily due to two viral proteins, E6 and E7, which by intracellular binding to p53 and retinoblastoma proteins prevent apoptosis and provoke unregulated proliferation (12). Infection with HPV can cause low- or high-grade intraepithelial lesions that usually heal without intervention, though persistent infections may progress to cancer (13, 14). The risk of cervical cancer increases with the number of sexual partners, oral contraceptives and smoking (15-17).

Primary prevention by vaccination against HPV reduces the development of precancerous lesions by an estimated 80% (18) and cervical cancer by 70% (19). Bivalent, quadrivalent and ninevalent vaccines all protect against HPV types 16 and 18, which are the most common sub-types inducing precancerous lesions (20-22). In Sweden, vaccination is offered to girls 10-12 years of age and since 2020, also to boys.

The World Health Organization (WHO) has stated its ambition to reduce the incidence of cervical cancer to <4/100,000 during the 21st century through vaccination of 90% of all girls by the age of 15 (23). At the same time, Australia instigated an ambitious program of vaccination in 2007 (including boys in 2013) designed to attain this same goal somewhere between 2021 and 2035 (24).

The nation-wide screening program in Sweden, updated in 2018, has effectively reduced the incidence of cervical cancer by identifying precancerous lesions, as well as early-stage tumors (19, 25, 26). All women between the ages of 23 and 65 are invited to participate. Women 30-65 years of age are tested for the presence of HPV, while those 23-29 years old are triaged for testing for precancerous lesions with liquid-based cytology and, if the findings are positive, are then tested for HPV (25). Ongoing research focuses on prevention with a vaccine directed against the viral proteins E6 and E7, which can hopefully even reverse precancerous lesions (27).

Unfortunately, the incidence of cervical cancer in Sweden increased by approximately 100 cases/year between 2014 and 2018 (28). Increased awareness of the unreliability of cytology testing alone has resulted in an updated screening program with more testing of HPV, which detects pre-stages of cervical cancer more accurately (25, 29). (*Figure 3*)

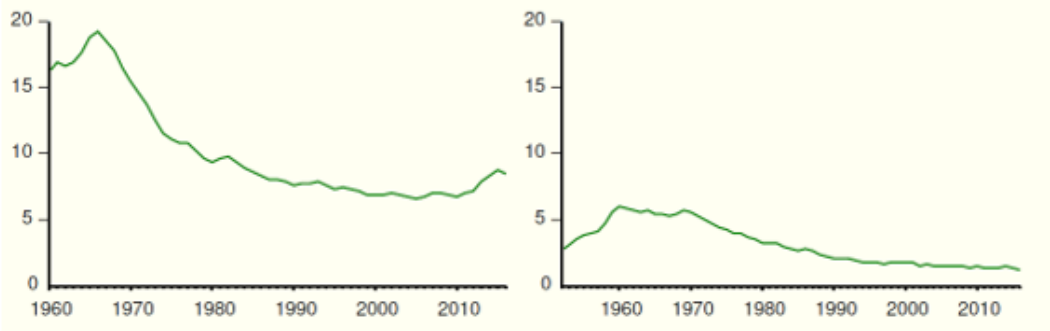


Figure 3. Incidence of cervical cancer /100000 population (left) and mortality from cervical cancer (right) in Sweden 1960-2010. Source: NORDCAN https://www-dep.iarc.fr/nordcan/sw/frame.asp

2.2 HISTOPATHOLOGY AND PROGNOSTIC FACTORS

The stage of the tumor and lymph node status are the most important independent determinants of the prognosis for women with cervical cancer. The 5-year survival for node -negative stage IB1 disease is approximately 95% but drops to 78% with node-positive disease (30, 31). The risk of lymph node metastases increases with larger tumors (32, 33) and a more advanced stage (34).

The two main histopathological types of cervical cancer are squamous cell carcinoma (75% of the cases in Sweden) and adenocarcinoma (25%). An increased incidence of adenocarcinoma has been reported and may partially be explained by the use of oral contraceptives (35, 36). Squamous cell carcinoma can be further categorized as keratinizing, non-keratinizing, basaloid, verrucous, warty, papillary, lymphoepithelioma-like or adenosquamous. The subtypes of adenocarcinoma include mucinous, endometroid, clear cell, serous, villoglandular and mesonephric. Other histopathological types, including neuroendocrine tumors, clear cell cancer and sarcoma, are rare and require individualized treatment.

Findings concerning whether histopathological type is associated with survival are inconsistent (30). However, the Swedish Quality Register for Gynecologic Cancer (SQRGC) recently reported that survival is independent of histopathological type (except for rare histotypes). Tumor extension beyond the cervix, e.g. involvement of the parametria, is known to be a risk factor for poor outcome (37). Other risk factors include involvement of the lymph vascular space (LVSI) and depth of invasion into the cervical stroma (38, 39). As is the case for most solid tumors, increasing age is associated with poorer prognosis, although there is no indication that the biology of the disease in younger and older women differs. However, younger women tolerate treatment better than the elderly (30).

2.3 STAGING

In the present thesis, staging of cervical cancer is based on the 2009 International Federation of Obstetrics and Gynecology (FIGO) classification (40) that preceded the current system (FIGO 2018) (41). In contrast to the more recent system, the classification from 2009, based on clinical examination under anesthesia, does not consider findings from advanced imaging, but does take into consideration the results of basic chest X-rays, urography, cystoscopy and/or rectal scanning (42).

Since the earlier clinical staging does not take into account the presence or absence of lymph node metastases, the actual stage of the disease was often underestimated (43, 44). Therefore, since January of 2020 (41), the new system of staging, including imaging in combination with clinical and histopathological findings is being utilized in Sweden (41). In addition, tumors <2 cm in size (IB1) are now considered separately from those 2-4 cm in size (IB2). For further information regarding the new staging system see *Table 1*.

Use of the Classifications of Malignant Tumors (TNM) in combination with the FIGO system is encouraged. The TNM involves standard classification of solid tumors on the basis of the size of the primary tumor, the involvement of regional lymph nodes, and the presence of distant metastases (45).

Table 1. Comparison of TNM classification of cervical carcinoma with staging according to FIGO in 2009 and 2018. Changes are marked in red. Adapted from (40, 41) and used with the kind permission of Dr. Pálsdóttir.

TNM	2018	2009	
T1	**I**	**I**	The carcinoma is strictly confined to the cervix (extension to the uterine corpus should be disregarded)
T1a		IA	Invasive cancer identified only microscopically (All gross lesions even with superficial invasion are Stage IB cancers). Stromal invasion is limited to maximal depth of 5 mm and width of 7 mm
T1a1		IA1	Measured invasion of stroma ≤ 3 mm in depth (and ≤ 7 mm width)
T1a1	1A1		Measured invasion of stroma ≤ 3 mm
T1a2		IA2	Measured invasion of stroma > 3mm and < 5 mm in depth (and ≤ 7 mm width)
T1a2	1A2		Measured invasion of stroma >3 mm and ≤ 5 mm
T1b		IB	Microscopic lesions > IA or macroscopic lesions limited to the cervix.
T1b	IB		Invasive carcinoma with measured deepest invasion ≥ 5 mm (greater than IA)
T1b1		IB1	Clinical lesions no greater than 4 cm in size
T1b1	IB1		Invasive carcinoma with ≥ 5 mm depth of stromal invasion, and largest dimension < 2 cm
T1b2		IB2	Clinical lesions > 4 cm in size
T1b2	IB2		Invasive carcinoma with a largest dimension ≥2 and <4 cm
T1b3	IB3		Invasive carcinoma ≥4 cm in largestdimension
T2	**II**	**II**	The carcinoma extends beyond the uterus, but has not extended onto the pelvic wall or the lower third of the vagina
T2a	IIA	IIA	Involvement of as much as the upper 2/3 of the vagina. No obvious parametrial involvement
T2a1	IIA1	IIA1	Invasive carcinoma with largest dimension <4 cm
T2a2	IIA2	IIA2	Invasive carcinoma with largest dimension ≥4 cm
T2b	IIB	IIB	Parametrial involvement, but not into the pelvic sidewall
T3	**III**	**III**	The carcinoma has extended onto the pelvic sidewall. On rectal examination there is no free space between the tumor and pelvic sidewall. The tumor involves the lower third of the vagina. All cases of hydronephrosis/nonfunctioning kidney should be included unless they are known to be due to other causes
T3a	IIIA	IIIA	Involvement of the lower vagina but no extension into the pelvic sidewall
T3b	IIIB	IIIB	Extension into the pelvic sidewall, or hydronephrosis/non-functioning kidney
TXN1	IIIC		Involvement of pelvic and/or paraaortic lymph nodes, irrespective of tumour size and extent (with r=radiology and p=pathology notations)
	IIIC1		Involvement of pelvic lymph nodes
	IIIC2		Involvement of paraaortic lymph nodes
T4	**IV**	**IV**	The carcinoma has extended beyond the true pelvis or has clinically involved the mucosa of the bladder and/or rectum The carcinoma has extended beyond the true pelvis or has clinically involved the mucosa of the bladder and/or rectum (Biopsy proven)
T4a	IVA	IVA	Spread to adjacent pelvic organs
T4b	IVB	IVB	Spread to distant organs

2.4 TREATMENT

The intent of primary treatment for early-stage cervical cancer is curative, with excellent survival regardless of treatment modality. There are two principally different treatment strategies: primary surgery or definitive chemoradiation (46). The only randomized controlled trial (RCT) comparing surgery and radiotherapy without concomitant chemotherapy was performed more than 30 years ago and included 343 patients with stage IB and IIA cervical cancer (52). No difference in survival was observed and no conclusion regarding preferred treatment drawn. Interestingly, primary surgery was associated with more morbidity and women who underwent surgery followed by adjuvant radiation did worst in terms of functional outcomes.

Maximal effort must be made to identify factors that indicate against treatment with both surgery and adjuvant radiotherapy (46). At the same time, surgery has remained the primary mode of treatment for tumors confined to the cervix and is recommended by most international societies. Surgery allows full nodal examination, the strongest prognostic factor, and chemoradiation can be reserved for treatment of recurrence. In a modern setting, the relevance of that earlier trial (46) is questionable, since both surgical and non-surgical treatments have been refined considerably. In addition, preoperative staging has improved dramatically, with the introduction of advanced imaging minimizing the risk of under-staging the disease.

In Sweden, definitive chemoradiation, including external beam radiation therapy (EBRT) in combination with intracavitary radiotherapy (brachytherapy) and weekly chemotherapy with cisplatin, is recommended for cervical cancer of stages IB3 and IIA2-IV4. The total external radiotherapic dose is 45-50 Gray (Gy) in the case of the lymph nodes and 50-56 Gy for the tumor target, both delivered at 1.8-2.0 Gy daily for 5-6 weeks (47, 48).

Early stages (IA1, IA2, IB1, IB2, IIA1 according to FIGO 2018 (41)) of cervical cancer are treated surgically by conization, simple hysterectomy or RH with pelvic lymphadenectomy (PLND), depending on the stage and characteristics of the tumor. In the case of stage IA1-2, conization or simple hysterectomy is sufficient, with supplementary PLND when LVSI is present. In tumors <2 cm in size and without aggressive histology, surgery designed to preserve fertility (trachelectomy) with pelvic lymph node assessment is an option.

Radical trachelectomy can be performed abdominally, vaginally or by MIS modalities, with all three approaches demonstrating oncologic safety comparable to that of traditional RH (49, 50). RH with PLND is recommended for stages 1B1-2 and IIA1. Although ovarian involvement is rare, removal of the ovaries (BSO=bilateral salpingo-oophorectomy) should be considered in

the case of adenocarcinomas and tumors with histological characteristics associated with high risk (51).

The indications for adjuvant treatment are primarily based on a RCT performed in 1999. Several adverse prognostic factors were identified and women with tumors larger than 4 cm, extension deep into the cervical stroma and LVSI benefited from adjuvant radiation (52). For high-risk tumors, Peters (54) found an improved OS with chemoradiation compared to radiation alone. The significance of close tumor margins has so far been poorly explored, but the general consensus is to offer adjuvant treatment when the margin is inadequate (< 5mm) (53, 54). The strongest prognostic factors for recurrence are stage, presence of lymph node metastasis and tumor size (33, 55). Adjuvant treatment has been demonstrated to reduce local recurrences in women with node-positive disease (56).

In an era of constantly evolving treatment options for women with early-stage cervical cancer, it becomes increasingly clear that current recommendations in this context are based on relatively weak scientific evidence. The few relevant RCTs were conducted more than 20 years ago (46, 52, 55) and do not reflect current practice. Notable changes during the past decades include the introduction of advanced imaging and MIS, addition of chemotherapy and refinement of external beam therapy (55, 57, 58). More recently advancements in brachytherapy, with the incorporation of image guidance and interstitial therapy, promise improved survival and QoL (59, 60). These changes should clearly be evaluated and considered with respect to the debate on surgical treatment of early-stage cervical cancer.

2.4.1 Surgical treatment of cervical cancer

In addition to traditional laparotomy (61), there are several surgical approaches to RH, including vaginal radical hysterectomy (62), MIS by conventional laparoscopy (63) and robot-assisted laparoscopic surgery (RRH) (64, 65).

The primary aim of surgery is to achieve tumor-free margins and thereby cure the patient. Adequate staging for prognostic purposes, as well as for deciding about whether to give adjuvant treatment is also essential. Considering that surgery is reserved for tumors confined to the cervix, the balance between radicality and the risk of morbidity is critical.

2.4.1.1 Radical hysterectomy

Radical hysterectomy, first performed by JG Clark in 1895 at Johns Hopkins School of Medicine (9, 66), has become the cornerstone of surgical treatment for early-stage cervical cancer. In order to achieve tumor-free margins when the tumor extended beyond the cervix and involved adjacent tissue, modification of the simple hysterectomy was necessary. The concept of RH was refined and described by the Austrian surgeon Ernst Wertheim in 1912, whose 500 patients had an extraordinary 5-year survival rate of 42% and only 18% mortality (66). In Japan, Hidekazu Okabayashi modified the technique further to include more extensive resection of the parametrial tissue through complete separation of the posterior leaf of the vesicouterine ligament to separate the ureter from the bladder (67).

The improved local control provided by lateral extension of the RH (*Figure 4*) raised the awareness of the importance of regional lymph node assessment. In the 1950´s Joe Vincent Meigs added bilateral systematic dissection of lymph nodes in the pelvis (68). The indication for PLND remains diagnostic (34, 69), although relatively recent studies from Germany suggest that "therapeutic lymphadenectomy" is an alternative to adjuvant radiotherapy for node-positive disease (70, 71).

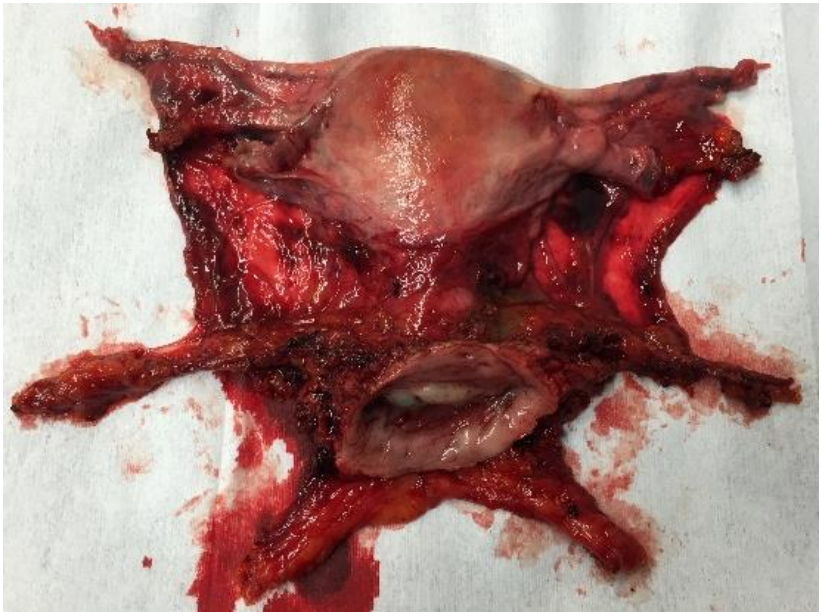


Figure 4. Surgical specimen from a radical hysterectomy including uterus with adnexa and surrounding parametrial tissue and opened vagina.

Growing awareness of the sequelae observed after RH led to the development of a nerve-sparing technique by the Japanese Takashi Kobayashi, where the splanchnic nerve was identified during dissection of the parametria (66). More recently, a novel concept related to compartmental dissemination of cervical cancer was proposed by Michael Höckel and co-workers (72). Based on the hypothesis that tumors initially spread within their own morphogenetic unit, a procedure referred to as total mesometrial resection (TMMR) that can also be applied to locally advanced tumors (IIB) was developed. TMMR is accompanied by therapeutic lymphadenectomy and even though node-positive disease is not treated by radiotherapy, survival is equally good or better than that reported following standard RH with postoperative radiation (70).

The lateral extension of hysterectomy first described by Wertheim was motivated by the observation that most cervical tumors extend beyond the cervix. With modern imaging, locally advanced tumors can be identified and subsequently treated with chemoradiation, a change that has prompted discussion about whether RH is still an appropriate treatment. Indeed, several studies, including an RCT, have demonstrated that survival following less radical surgery is no worse than with standard RH (73-76).

Data on the safety of treating small tumors (<2 cm) in the absence of other risk factors with less radical surgery is available (74, 77, 78). Parametric involvement is extremely rare with tumors less than 2 cm in size (≤IB1) and for these, surgical treatment with simple hysterectomy appears to be sufficient. In the ongoing SHAPE trial, for which results are expected in 2021, women with stage IA-IB1 disease are randomized to undergo either simple or radical hysterectomy (79). It has also been proposed that radical surgery can be replaced by neoadjuvant chemotherapy followed by fertility-preserving surgery (80).

Historically, RRH was classified according to Piver-Ruthledge system (81), but in 2009 Querleu-Morrow introduced a new system that takes into account the three- dimensional anatomy of the pelvis (82). (*Table 2*)

The European Society of Gynaecological Oncology (ESGO) has published guidelines in an attempt to improve and standardize the management of cervical cancer, where quality indicators such as disease recurrence < 10% in T1bN0 within 2 years after primary surgical treatment (83).

Table 2. Classification of radical hysterectomy according to Querleu-Morrow (82)

Type	Resection	Mobilization of the ureter	Lateral dissection	Vaginal resection	Involvement of the sacrouterine ligament	Involvement of the vesicouterine ligament
A	Extra fascial	None	Close to the cervix	Minimal resection	Dissection close to the cervix	Dissection close to the cervix
B	Modified radical	Partial	Medial to the ureter	10 mm	Partial resection	Partial resection
C1	Classic radical	Complete	Lateral to the ureter. At the iliac vessels caudal part preserved	15–20 mm	Transection at the rectum Nerve-sparing	Transection at the bladder Nerve-sparing
C2	Classic radical	Complete	Lateral to the ureter. At the iliac vessels including caudal part	15–20 mm	Transection at the rectum Hypogastric nerve is sacrificed	Transection at the bladder Bladder nerves sacrificed
D	Lateral extended	Complete	At the exit of the *a. iliaca interna*, with exposure of the root to *n. ischiadicus*	15–20 mm	Transection at the rectum	Transection at the bladder

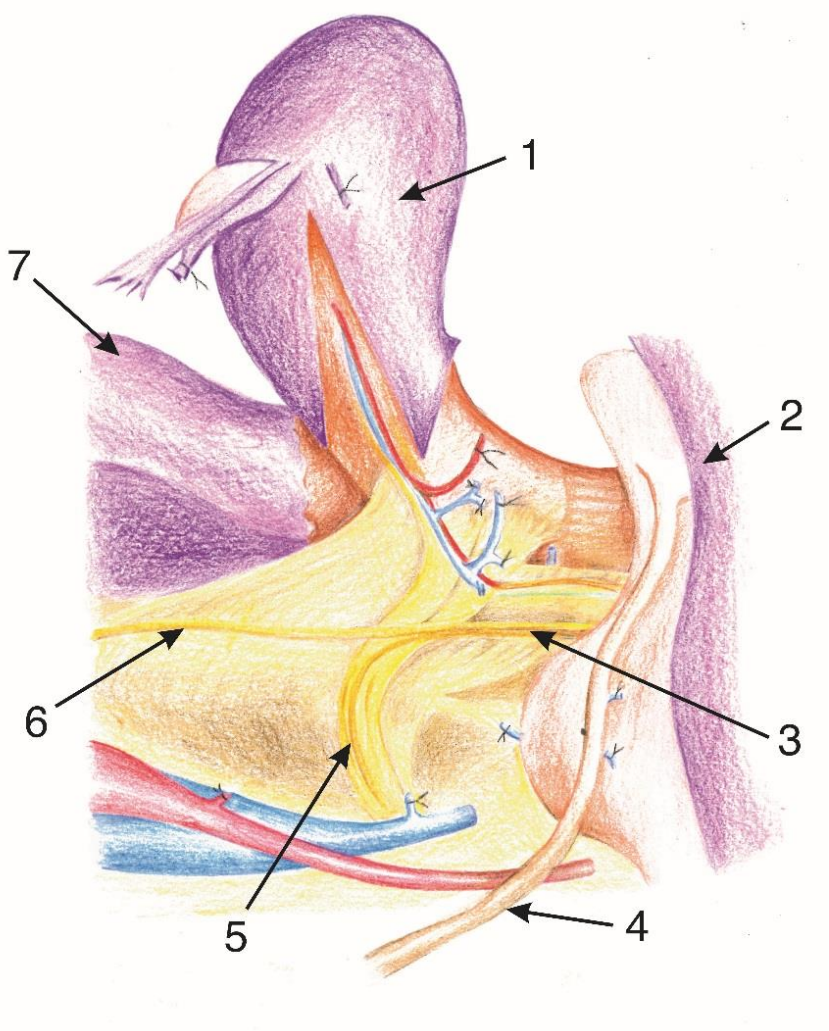
2.4.1.2 Nerve-sparing radical hysterectomy

The uterus, urinary bladder, distal rectum and upper vagina are innervated by both the sympathetic and parasympathetic branches of the autonomic nervous system. The nerves of greatest importance are the sympathetic nerve fibers from the hypogastric nerve plexus and parasympathetic nerves from the pelvic splanchnic system (sacral roots S2-S4). The hypogastric plexus is divided into the inferior hypogastric nerve that follows the ureter past the sacrouterine ligaments. At the cardinal ligaments, the hypogastric fibers fuse with the pelvic splanchnic nerve (84).

For maintaining bladder function both sympathetic and parasympathetic autonomic nerves must be preserved, including the hypogastric nerve, pelvic splanchnic nerve, inferior hypogastric plexus and vesical branches of the inferior hypogastric plexus. Unfortunately, certain aspects of RH can damage these important nerves (*Figure 5*). The transection of the uterosacral ligament may injure the hypogastric nerve and the splanchnic nerve needs to be identified during the dissection of the cardinal ligament (the lateral parametrium). Also, the inferior hypogastric plexus may be injured when the surgeon ligates and divides the vaginal blood vessels (85, 86).

There are studies suggesting that nerve-sparing techniques reduce functional problems after RH (87-92). The modified classic RH, the type C1, is theoretically nerve-sparing if performed

according to the anatomical boundaries as described by Querleu-Morrow in 2008. In 2011, Cibula added a more precise description of the parametrial resection (82, 93).



1.Uterus
2. Bladder
3. Inferior hypogastric plexus
4. Ureter
5. Splanchnic nerve
6. Hypogastric nerve
7. Rectum

Figure 5. Nerves at risk during RRH. Adapted from (94), modified by M Santos.

2.4.1.3 Minimally invasive radical hysterectomy

The first laparoscopy was described in 1805 when Phillip Bozzini developed a cystoscope to examine canine bladder. Later, the Swedish surgeon Hans Christian Jacobaeus performed an experimental laparoscopic procedure in a dog. In the 1930s laparoscopy gained popularity in the US as a less invasive alternative to laparotomy and in1936, the first laparoscopic sterilization was performed by dr Boesh, a Swiss gynecologist (95). During the 1980´s, the

introduction of the video laparoscopy together with the development of better instruments revolutionized the technique (96). The first laparoscopic hysterectomy was performed in the late 1980s and large RCTs has later established the benefits of laparoscopy compared to traditional open hysterectomy for endometrial cancer (97-99). The first laparoscopic RH was described in 1992 (100) and subsequent case-series reported less postoperative pain and a shorter hospital stay (63, 100-108) compared to ORH. Two meta-analyses of retrospective data suggested superior outcomes for MIS. Wang with colleagues included twelve original studies (1539 women) comparing LRH with open technique where OS was similar between the two surgical modalities (92). In the same year, 2015, Shazly with colleagues included 26 nonrandomized studies comparing MIS (LRH and RRH) with ORH and concluded better surgical outcomes for MIS as lower blood loss, shorter hospital stay. However, conventional laparoscopic RH has never been widely adopted in Scandinavia due to the relatively long learning curve, as well as ergonomic disadvantages (109, 110).

In 2005 robot-assisted laparoscopy (RRH) was first approved by the Food and Drug Agency (FDA) for gynecological indications in the United States. The technology was rapidly adopted worldwide and in Scandinavia despite the high costs associated with the technology. Compared to traditional laparoscopy, robot-assisted laparoscopy offers improved visibility and greater surgical precision, as well as ergonomic advantages for the surgeon (111), less or similar complications and faster recovery (112, 113). The first RRH was performed in 2005 (114) and early experiences suggested benefits compared to the traditional open procedure in terms of shorter hospital stays, fewer complications and less blood loss (65, 101, 107, 110, 115-122).

Observational studies further indicated that the oncologic outcomes following RRH and open procedures were similar (102, 107, 116, 118, 123-125). Most international societies including Swedish national guidelines (19), as well as the National Comprehensive Cancer Network (126) and ESGO (127), considered MIS to be safe and the recommended surgical approach for early cervical cancer, although RCTs were lacking. In 2008, the international, randomized controlled trial "Laparoscopic Approach to Cervical Cancer" (the LACC-trial) was initiated to explore the oncologic safety of MIS for early stage cervical cancer (128). The enrollment of study subjects was slow, and data was not available until 2018 after premature closure. In agreement with the results from the LAP2 and LACE trials, the LACC-trial was expected to show non-inferiority for MIS (97, 98).

The LACC-trial finally enrolled 632 women with stage IA-IB1 cervical cancer and the primary endpoint was disease-free survival (DFS) at 4,5 years. The trial was never completed since the Data Safety and Monitoring Board observed a dramatic difference in DFS with inferior

outcome in the MIS arm compared to open approach (86.0% versus 96.5%, HR 3.74; 95% Cl, 1.63-8.58) (1). In addition, the MIS arm was associated with an inferior OS of 93.8 % vs 99.0%, HR 6.00; 95% Cl, 1.77-20.30). The trial was immediately criticized on several aspects. The main criticisms include the subjective assessment of surgical proficiency, the lack of central pathology and the slow accrual of study subjects from a total of 33 centers. In addition, the LACC-trial did not explicitly explore the safety of RRH and only 15.6% underwent this approach in the MIS arm.

The surprising findings from the LACC trial have since the publication in 2018 been reinforced by observational data (129-133) (*Table 3*). Based on data from the National Cancer Database between 2010-2013 including 2203 women with stage 1A2-1B1 cervical cancer in the United States, Melamed observed a 9.1% risk of death after MIS compared to a corresponding risk of 5.3% after open surgery (HR 1.65, p=0.002) (2). A recent metanalysis included 15 high-quality retrospective studies encompassing 9499 patients, of whom 2675 underwent RRH, 2009 LRH and 4815 open surgery. The risk for recurrence or death after MIS was concluded to be higher than after open technique (HR 1.71, p<0.001). In a stratified analysis of the studies predominated by RRH, a higher risk of recurrence or death (HR 1.88 (Cl 1.36-2.60) was observed. In addition, a similar analysis of studies of LRH, the HR was found to be 1.54 (Cl 1.10-2.16) Interestingly, only one out of five papers published prior to the LACC-trial suggested that RRH was inferior to ORH (134).

Secondary endpoints from the LACC-trial have recently been published and challenge the perceived benefits of MIS for cervical cancer. In line with RCTs in endometrial cancer, most retrospective data have indicated that MIS confers less perioperative morbidity. However, no difference in either intra- nor postoperative adverse outcomes was observed in the LACC-trial (135). Interestingly, more nerve injuries and vaginal vault complications were observed in the MIS arm and as expected, a higher frequency of transfusions and wound complications in the open arm.

Based on the results from the LACC-trial, RRH is no longer considered to be the standard treatment for early cervical cancer and most societies and national guidelines have changed their recommendations in favor of ORH (3, 4).

Table 3. Comparative studies regarding oncologic outcome of RRH and ORH

Study (year of publication)	**Number of MIS performed (% RRH)**	**Number of ORH performed**	**Period of study**	**Type of study**	**Follow-up RRH/ORH (months)**	**Number of deaths MIS/ORH**	**Number of recurrences MIS/ORH**	**Risk of recurrences or death HR (95%CI)**
Ramirez (1)[3] (2018)	319 (16)	312	2008-2017	RCT	54	19/3	27/7	3.74 (1.63-8.58)
Shah (121)[1,2] (2017)	109 (100)	202	2001-2012	RM	31/31	13	32	1.60 (0.75-3.43)
Wallin (117)[1,3] (2017)	149 (100)	155	2006-2015	RS	36/88	6/15	36	2.13 (1.06-4.26)
Melamed (2)[1,3] (2018)	1236 (79)	1225	2010-2013	RM		164	NR	1.65 (1.22-2.22) (OS)
Alfonzo (136): [1,2] (2019)	232 (100)	232	2011-2017	RP	44.5/56	32	55	1.08 (0.66-1.78)
Doo (130)[1,3] (2019)	56 (100)	49	2010-2016	RS	25/25	10	20	2.63 (1.05-6.67)
Chen (131)[1,3] (2020)	1048 (100)	9266	2004-2016	RM	24/48	879	NR	2.34 (1.54-3.56)
Uppal (132)[1,3] (2020)	156 (88)	159	2010-2017	RS	31/48	13	25	2.83 (1.10-7.18)
Hoogendam (102) (2014)	100	0	2008-2013	RS	30	NR	13	81.4% PFS 88.7% DSS
Zantagnolo (118) [2] (2016)	203 (100)	104	2006-2014	RS	26/50	NR	29	8.8% RRH 10.6% ORH p=0.63
Sert (125) (2011)	42 (83)	26	2005-2009	RS	33/70	1 in RRH	5 in RRH	NR
Sert (107) [2] (2016)	259	232	2005-2011	RM	35/45	23/21	7/9	9% recurrence in both groups
Cantrell (123)[2] (2010)	63	64	2005-2008	RS	12	NR	1/7	RRH: PFS 94 % ORH: PFS 89% p=0.27
Mendivil (116) [2] (2016)	107 (55)	39	2009-2013	RS	39	NR	17	PFS: RRH 89.7% LRH 89.7% ORH 84.6% p=0.27
Gil-Moreno (115) [4] (2016)	112 (20)	76	1999-2016	RS		NR	NR	OS MIS 91% ORH 78.9% p=0.026
Cusimano (133) [3] (2019)	473(10)	483	2006-2017	RS	60/72	NR	57/53	1.97 (1.10-3.50)

[1] Included in metanalyses by Nitecki (134)
[2] No difference in oncologic outcome RRH (MIS)/ORH
[3] Better oncological outcome with ORH
[4] Better oncological outcome with MIS
RCT = randomized controlled trial; RS = Retrospective single-center; RM = Retrospective multi-center; RP = Retrospective population based; PM = Prospective multi-center; NR: not reported; HR=Hazard Ratio; CI=confidence interval; OS=overall survival; PFS=progression-free survival

2.4.2 Lymph node assessment

RH includes assessment of pelvic lymph nodes in order to identify regional tumor dissemination. Traditionally, systematic PLND, including the external iliac and obturator area, has been recommended for early-stage cervical cancer. In agreement with staging procedures for other malignancies, lymphadenectomy is associated with substantial morbidity, with lymphedema being the most important (137, 138). In addition, during PLND, nerve damage may occur and injuries to large vessels have been reported (139). Persisting lymphedema has a substantial impact on QoL and treatment options are limited (137, 140, 141).

In connection with treatment of breast cancer, systematic lymphadenectomy has been replaced by detection of sentinel lymph nodes (SLN), which reduces morbidity dramatically (142). For cervical cancer, several investigations studies suggest that the adoption of SLN technique is feasible and allows highly sensitive detection of metastatic disease (143-145). Replacement of Tc99 with the novel tracer indocyanine green (ICG) has simplified the procedure considerably (146). In addition to the expected reduction in postoperative lymphedema, SLN allows improved histopathological analysis based on ultrastaging of retrieved nodes. However, survival data is lacking and results from an ongoing RCT comparing SLN with full lymphadenectomy (SENTICOL III) are not expected until 2027 (147). Based on current evidence, ESGO recommends usage of SLN only for stage IA cervical cancer and the recently revised Swedish guidelines include similar recommendations (127, 148).

2.5 HEALTH CARE COSTS ASSOCIATED WITH SURGICAL TREATMENT

Although the Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) has described methods for calculating health care economics, no authority evaluates the costs of technical medical products used in Sweden (149). It is clear that the total cost for robot-assisted surgery in prostate cancer is higher than for traditional laparotomy (150, 151). Moreover, Lönnerfors and colleagues (152) concluded that robot-assisted surgery for benign indications is associated with higher costs and several studies have shown that this is also the case for endometrial cancer (153, 154). However, Reynisson and Persson found that cost effectiveness for RRH can be achieved in high-volume settings (155). Clearly, comparison of different economic studies of this type is challenging because the costs included vary widely. Nonetheless, financial considerations remain a major concern when new technologies are introduced into the clinic (156).

2.6 FUNCTIONAL OUTCOMES AFTER SURGICAL TREATMENT OF CERVICAL CANCER

Traditionally, evaluation of cancer therapy in clinical trials has been based on disease-free (DFS) and overall survival (OS), tumor response, and toxicity, but in the past few decades there has been an increased focus on the patient´s QoL, which is now also frequently assessed in clinical trials (157). The term QoL and, more specifically, Health Related Quality of Life (HR-QOL), encompasses perceptions of both negative and positive aspects of at least physical, emotional, social and cognitive functions (158). In addition, QoL has been proposed to have an impact on survival (159).

HR-QoL is assessed subjectively through questionnaires of varying validity (i.e., measuring what is intended to be measured) and reliability (i.e., absence of errors). In cancer patients, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaires (EORTC QLQ-C30), has been developed (160). This 30-item multidimensional questionnaire whose validity and reliability have been confirmed in several studies (161, 162), is frequently employed.

There are also two instruments designed specifically to assess the QoL of patients with cervical cancer. The first of these is the Quality of Life module of the European Organization for Research and Treatment of Cancer, EORTC QLQ-CX24. This consists of 24 questions designed to evaluate body image, sexual activity and enjoyment, sexual and vaginal functioning, as well as symptoms associated with sexual experience, peripheral neuropathy, menopausal status, lymphedema, and sexual anxiety (163). In addition, the Functional Assessment of Cancer Therapy (FACT-Cx) was designed to assess the health-related quality of life of patients with cervical cancer (164).

Most commonly, questionnaires are validated psychometrically. However, even if a psychometrically valid instrument describes the symptoms reliably, it is not designed to elucidate underlying causes. For this reason, Professor Gunnar Steineck at Sahlgrenska Academy developed a clinimetric approach for validation (165, 166). In this context each question undergoes an extensive face-to-face validation (sometimes called the “think-aloud-method”) to ensure that the respondents understand correctly. Moreover, when the response rate has been too low in preparatory studies, the phrasing of questions has been adjusted to improve this situation. The questionnaire used in **Study III** has been validated employing Steineck´s approach.

2.6.1 Psychological quality of life

Results concerning the psychosocial well-being among survivors of cervical cancer have varied widely, due to differences in the questionnaires used, as well as the heterogeneity of participants with respect to tumor stage and treatment (167, 168). Following treatment, anxiety and mental fatigue are common (169-171), as is impaired fertility, which in itself is a risk factor for depression (172). Some studies have reported a higher incidence of divorce (173). A systematic review published in 2019 and including women in the Nordic countries who developed gynecological cancer concluded that even many years after treatment, these patients can still exhibit lowered physical, mental and psychosocial well-being (174).

In colon cancer, RCTs support that MIS does not affect HR - QoL to the same extent as open surgery (175, 176). However, in gynecological cancer, the evidence to date reveals no difference between RRH and ORH (177, 178). The LACC trial support the conclusion that QoL following treatment of cervical cancer with MIS or open surgery does not differ (179).

2.6.2 Sexual function

Survivors of cancer are at risk of impaired sexual function with reduced desire, arousal and sexual satisfaction (166, 180-182). This is also the case for women who undergo ORH for cervical cancer. Decreased desire can probably be explained, at least in part, by the stress associated with diagnosis and treatment. However, if autonomous nerves are damaged during the surgical procedure, vaginal blood flow, swelling of the genitals and lubrication may also be reduced (88, 182-186). Furthermore, following treatment the vagina can become shortened and less elastic due to fibrosis and adhesions, leading to pain during intercourse (166, 187, 188). Such symptoms have been observed after both ORH (88, 182) and LRH (89, 111, 189). A systematic review published in 2012 concluded that impaired sexual function in survivors of cervical cancer is almost always accompanied by pain during intercourse, while the capacity to experience orgasm (sexual satisfaction) often remains intact. Therefore, impaired arousal could be primarily a result of dyspareunia. Again, comparison of the results of different investigations on the QoL and sexual function of survivors of cervical cancer is challenging because of the variety of questionnaires used and differences in the inclusion criteria and, consequently, in the patient populations involved (190).

2.6.2.1 Assessment of sexual function

Female sexual function can be assessed with questionnaires, interviews and/or log books. Due to the shortage of validated questionnaires in this area, it is difficult to compare the results of different studies. In addition, the multi-dimensional nature of sexual function, with its

psychological, physiological and cultural aspects, even makes it more challenging to assess. The Female Sexual Function Index (FSFI) has been validated under a range of clinical conditions, including cervical cancer, and is widely used. It is available in Swedish (191, 192). However, this index has only been validated for sexually active, and not for sexually inactive women. Two other questionnaires in this area, the Leiden Questionnaire (193) and the Sexual Function–Vaginal Changes Questionnaire (194), have still to be validated for use in Sweden.

Objective assessment of genital response through determination of local blood flow in the vagina with photoplethysmography has shown that RH reduces this blood flow more than simple hysterectomy (195, 196). Attempts have been made to measure the clitoral volume by MRI (197) or assess the temperature of the labia during sexual stimulation (198).

2.6.3 Bladder function

Bladder function consists of storage and voluntary voiding. Voluntary voiding involves relaxation of the internal urethral sphincter and contraction of the detrusor muscle, thereby permitting micturition mediated by the parasympathetic nervous system. On the other hand, during storage the sympathetic fibers relax the bladder muscle and contract the internal sphincter, thus inhibiting micturition (199). The sensory pelvic and hypogastric nerve fibers transmit information about bladder fullness.

Bladder dysfunction after RH is common, being reported by as many as 70% of those undergoing such treatment (199-201). Both early postoperative bladder dysfunction (increased post-voidal residual volume, lowered detrusor activity, reduced bladder sensation, decreased maximal urethral closure pressure) as well as long-term complications (such as voiding only with abdominal straining, a larger post-voidal residual volume (PVR), an over-active detrusor and urinary incontinence due to stress) are common (87, 199, 201). However, the causes of this bladder dysfunction have not yet been completely investigated. Studies on cadavers have revealed a high incidence of nerve injury in association with resection of the uterosacral and vesicouterine ligaments, as well as of the paracervical tissue during RH (86). Thus, damage to parasympathetic nerves is believed to explain this dysfunction, at least in part (87-92). A RCT study from Korea reported that fewer nerves had been ablated in the patients undergoing nerve sparing surgery, who also had better bladder function (188). However, alternative explanations for bladder dysfunction include anatomical repositioning of the bladder, postoperative edema and inflammation, all of which decrease bladder compliance (84).

2.6.3.1 Assessment of bladder function

Bladder function can be assessed subjectively with validated questionnaires. Objective evaluation of the bladder is performed by a standardized urodynamic examination using both a urethral and abdominal (placed rectally) sensors. This allows determination of urethral pressure, voiding volume, post-void residual volume, maximal flow rate, and voiding time. These measurements result in a cystometrogram (documenting the volumes associated with first sensation and first desire to void, bladder capacity and filling rate, potential over-activity of the detrusor muscle, stress incontinence, and the abdominal pressure at which leakage occurs), as well as a profile of urethral pressure (202, 203). (*Figure 6*)

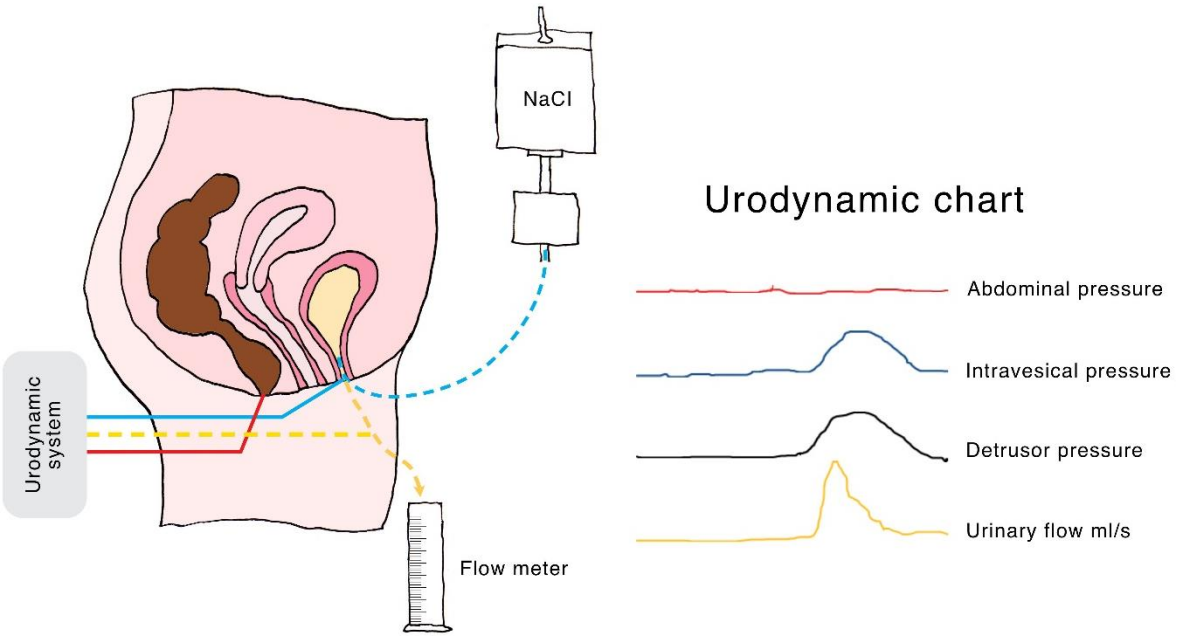


Figure 6. Schematic overview of urodynamic investigation

2.6.4 Bowel function

Several studies based on patient questionnaires report impaired bowel function as a result after ORH. The symptoms, including constipation, urge to defecate, flatulence and fecal incontinence, can be extremely stressful (204). Potential causes are surgical damage to nerves, as well as post-operative adhesions and fibrosis (88, 205, 206).

2.6.5 Lymphatic function

PLND involves the removal of lymph nodes from the external and internal iliac vessels and obturator space. Accumulation of lymphatic fluid and chronic inflammation in the subcutaneous fat is observed in 12-25% of women after RH for early cervical cancer with a negative impact on QoL (137, 138, 140, 141). This complication can be assessed subjectively by patient-reported questionnaires and objectively by measuring the circumference of the thigh before and after surgery. Lymphangiography may add information in select cases (207).

2.7 SEX STEROID HORMONES AND CERVICAL CANCER

2.7.1 Ovarian sex steroids

Production of sex steroid hormones (estrogens, progesterone and androgens) by the ovaries and adrenal cortex is regulated via the hypothalamic-pituitary-ovarian and hypothalamic-pituitary-adrenal axes. Gonadotropin-releasing hormone (GnRH) synthesized in the hypothalamus stimulates the production of both gonadotropin luteinizing hormone (LH) and follicle-stimulating hormone (FSH) by the pituitary. Subsequently, LH and FSH stimulate secretion of sex steroid hormones from the ovaries (208). Removal of the ovaries in premenopausal women reduces their levels of estrogen dramatically, causing postmenopausal symptoms.

2.7.2 Anti-Müllerian hormone

Anti-Müllerian hormone (AMH), a glycoprotein produced by the granulosa cells during the early development of follicles, is considered to be an indicator of the number of follicles remaining in the ovaries (209) and declines by 0.16 ng/mL each year among women of fertile age (210). Following ORH with preservation of the ovaries, the level of AMH declines by 45% (211), probably because the surgery impairs the blood supply to the ovaries. **Study III** reports the first evaluation of the impact of RRH on ovarian function.

2.7.3 Androgens

Production of androgens (testosterone, androstenedione and dehydroepiandrosterone) by the ovaries and adrenal cortex is regulated by the hypothalamus. In women, approximately 25-50% of circulating testosterone originates from the ovaries (212) and bilateral salpingo-oophorectomy is associated with a 15-50% decline (213, 214). Even when the ovaries are not removed, surgery reduces the levels of circulating testosterone in women (211), most likely due to impairment of the ovarian blood supply. In this context the effect of robot-assisted surgery has yet to be explored.

In both men and women, testosterone plays a key role in sexual desire and arousal through its direct effects on the central nervous system, as well as by increasing genital blood-flow (215, 216). At the same, a direct link between serum levels of testosterone and sexual function in women has not yet been proven (217).

3 AIMS OF THE PRESENT THESIS

The overall aim of this research project was to assess the oncologic and surgical outcomes after RRH and to investigate the functional consequences of RRH for early-stage cervical cancer.

The specific aims were as follows:

Study I

- To compare RRH and ORH performed at KUH with respect to surgical and oncologic outcomes as well as health care costs

Study II

- To compare overall (OS) and disease-free survival (DFS) following ORH and RRH for early-stage cervical cancer at the national level

Study III

- To characterize the impact of RRH on sexual, bowel and bladder function, as well as on the lymphatic system one year after treatment
- To assess psychological well-being one year after RRH
- To examine the effect of RRH on ovarian function

Study IV

- To examine whether ablation of pelvic nerves and subjective and objective bladder dysfunction following RRH for early-stage cervical cancer are correlated.
- To investigate the association between patient-reported outcomes and objective characterization of bladder function, as well as quality of life during the first year after RRH.

4 PARTICIPANTS AND METHODS

In Sweden treatment of cervical cancer is performed at one of the 7 university hospitals (tertiary centers) or other regional hospitals. KUH alone serves the entire Stockholm region, with its current population of 2.4 million, and has treated all cases of cervical cancer among women in this region since 2004.

Study I is a retrospective analysis of 304 women in the Stockholm region who underwent RRH or ORH. **Study II** involves a nationwide cohort of 864 women who underwent RRH or ORH. **Studies III and IV** are prospective follow-up studies of 26 and 27 women, respectively, in the Stockholm region who underwent RRH (*Table 4*).

*Table 4. Overview of **Studies I-IV***

Variables	Study I	Study II	Study III	Study IV
Type of study	Register-based	Register-based	Prospective	Prospective
No of participants	304	864	26	27
Setting	KUH	Sweden	KUH	KUH
Treatment	ORH/RRH	ORH/RRH	RRH	RRH
Period of inclusion	Jan 2006- Dec 2015	Jan 2011- Dec 2017	Nov 2011- Dec 2013	Nov 2011- Dec 2013
Type of radical hysterectomy[1]	B	B/C	B	C1
Follow-up (months)	88.7 (ORH) 35.7 (RRH)	55.7 (ORH) 44.5 (RRH)	12	12
Sources of information	Orbit[2] Medical charts	SQRGC Medical charts	Questionnaire Blood samples	Questionnaires[3] Urodynamics Nerve biopsies
Outcome assessment	Surgical PFS OS Health Care Costs	OS DFS	Sexual-, Bladder-, Bowel-, Lymphatic-function Sex hormones	Bladder function QoL Number of ablated nerves

[1]According to Querleu-Morrow (82); [2]Orbit = The hospital data base for surgical procedures;
[3]LUTSqol and FLUTS
KUH = Karolinska University Hospital; ORH open radical hysterectomy; OS = Overall Survival; DFS Disease-free survival; QoL = Quality of Life; SQRGC = Swedish Quality Registry for Gynecological Cancer

4.1 PARTICIPANTS AND SETTING

The characteristics of the patients involved in **Studies I** and **II** are shown in *Table 5*, with *Table 6* presenting the same information for **Studies III** and **IV**.

*Table 5. Patient and tumor characteristics **Studies I and II***

Variables	**Study I (n=304)**		**Study II (n=864)**	
Treatment (n)	ORH (155)	RRH (149)	ORH (236)	RRH (628)
Patients				
Age in yrs, median (range)	42 (23-78)	43 (25-74)	46 (24-81)	42 (22-83)
BMI mean (range)	24 (16-41)	24 (18-46)	24.7 (17-47)	25 (17-60)
ASA≥3 n (%)	13 (8.4)	10 (7.4)	NR	NR
Tumors	n (%)	n (%)	n (%)	n (%)
Stage (FIGO 2009)				
IA1	13 (8.4) for	17 (11.4) for	8 (3.4)	36 (5.7)
IA2	both combined	both combined	21 (8.9)	61 (9.7)
IB1	128 (82.3)	129 (86.6)	207 (87.7)	531 (84.6)
IB2	7 (4.5)	1 (0.7)	0	0
IIA	7 (4.5)	1 (0.7)	0	0
Histology				
Squamous cell carcinoma	97 (62.3)	88 (59.1)	145 (61.4)	365 (58.1)
Adenocarcinoma	46 (29.7)	50 (33.6)	78 (33.1)	233 (37.1)
Other	12 (7.7)	11 (7.4)	13 (5.5)	30 (4.8)[2]
Size				
≤20mm	78 (50.3)	90 (60.8)	150 (63.6)	460 (73.2)
>20 ≤40mm	66 (42.6)	49 (33.1)	70 (29.7)	151 (24)
<40 mm	11 (7.1)	9 (6.1)	12 (5.1)	16 (2.5)

[1] *According to Querleu-Morrow (82)*
[2] *Only adenosquamous*
NR = not reported; BMI = body mass index (kg/m^2); ASA = American Society of Anesthesiologists

*Table 6. Patient and tumor characteristics (median (range) or n (%)) **Studies III and IV***

Variables	Study III (n=26)	Study IV (n=27)
Patients		
Age, year	44 (29-64)	43 (18.5-33.6)
BMI	27 (19-39)	43 (18.5-33.6)
Performance status	ASA 1 (1-3)[1]	ECOG 0 (0-0)[2]
Lymph node yield	18 (11-55)	NR
With partner at baseline	24 (92)	21 (78)
Single at baseline	2 (8)	6 (22)
Premopausal at baseline	22 (85) [3]	20 (74) [4]
Postmenopausal at baseline	4 (15) [3]	7 (26) [4]
Tumors		
Stage (FIGO 2009)		
IA1	0	0
IA2	1 (4)	2 (7.4)
IB1	24 (92)	25 (29.6)
IB2	1 (4)	0
IIA	0	0
Histology		
Squamous cell carcinoma	12 (46)	15 (55.6)
Adenocarcinoma	13 (50)	10 (37)
Other	1 (4)	2 (7.4)

[1] According to ASA = American Society of Anesthesiologists; [2]According to EGOG = Eastern Cooperative Oncology Group Performance Status (0-5); [3]Based on Follicle-stimulating hormone (E/L) ≤25; [4]Based on an age > 50 years; NR = Not Reported; BMI = body mass index (kg/m2)

4.1.1 Study I

All women who underwent RH and PLND for early stage 1A1-IIA1 cervical cancer at KUH from January 2006 to December 2015 (n=309) were initially included. Restriction to tumors of the squamous, adenocarcinoma or adenosquamous histological subtype led to exclusion of 5 of these. The inclusion of patients is illustrated in *Figure 7*.

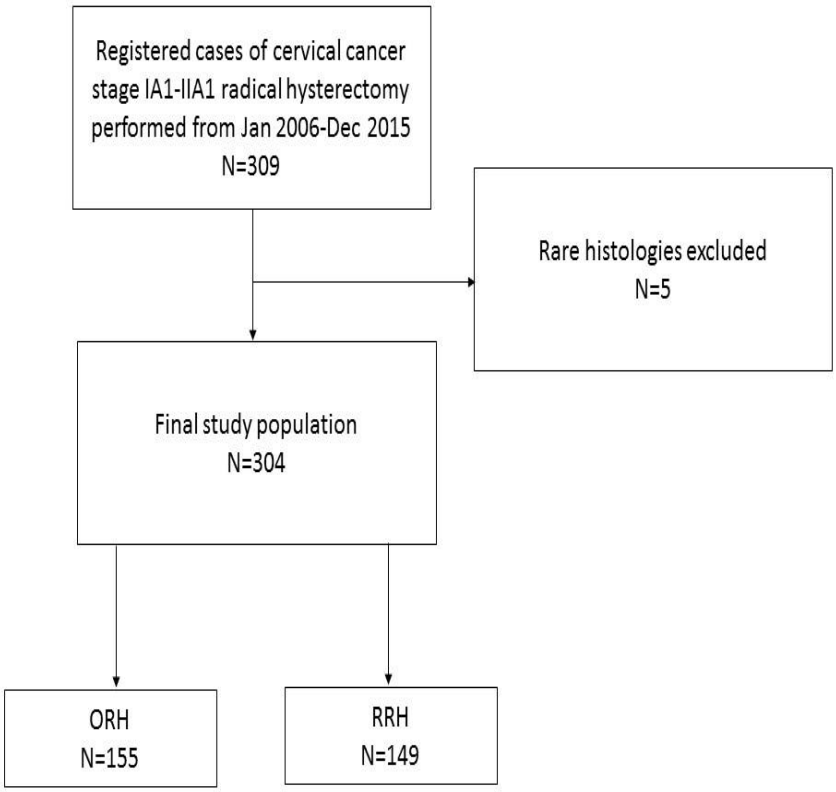


*Figure 7. Flow chart illustrating the selection of patients for inclusion in **Study I***

4.1.2 Study II

All women in Sweden older than 18 years and scheduled to undergo RH (type B or C as classified according to Querleu-Morrow (82)) for FIGO stage IA1-IB cervical cancer from January 2011 to December 2017 (n=967) were considered for inclusion. The inclusion process, including the criteria for exclusion, are illustrated in *Figure 8.*

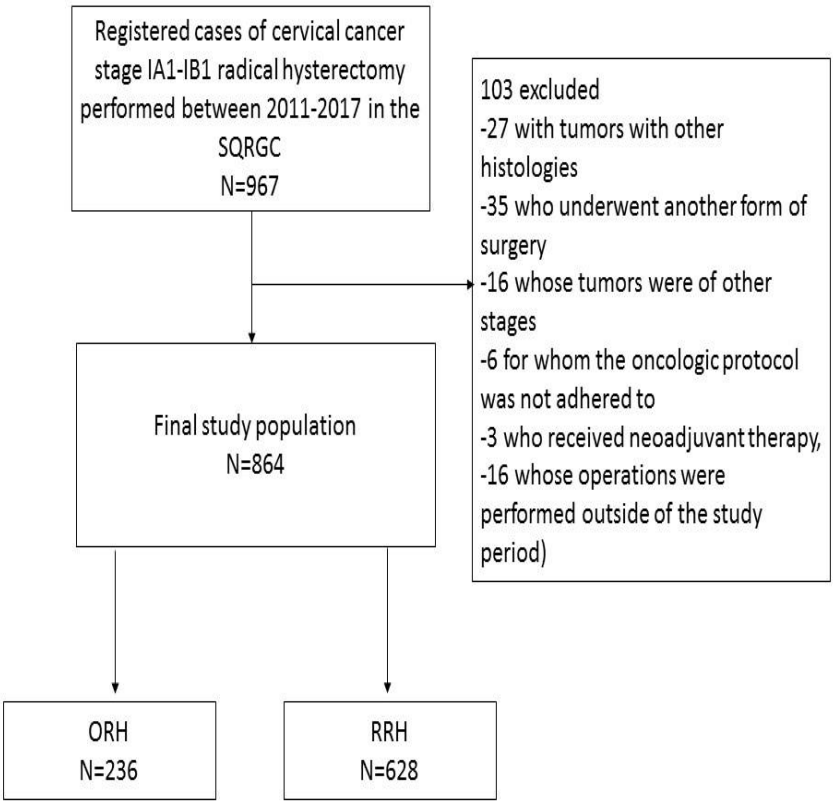
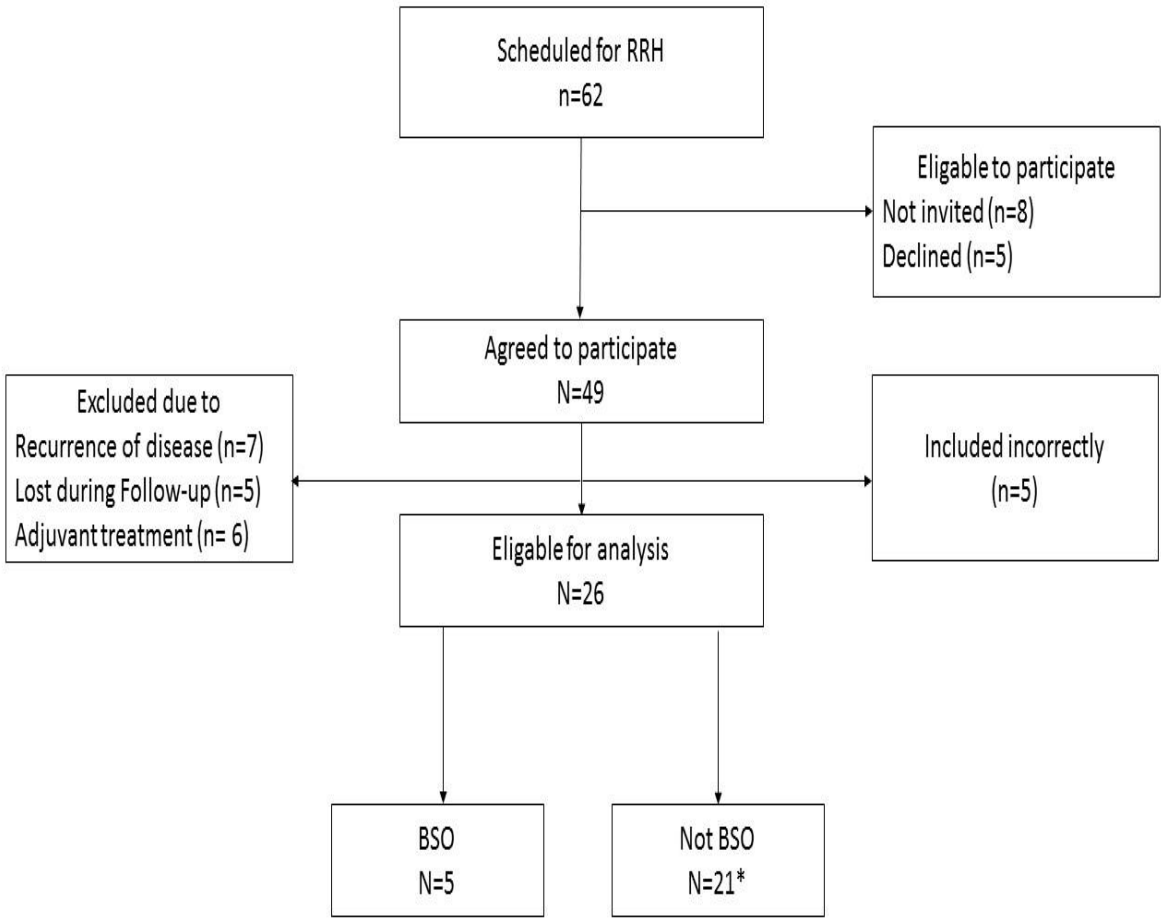


Figure 8. Flow chart illustrating the selection of patients for inclusion in ***Study II***

4.1.3 Study III

Women aged 18-75 scheduled for RRH for stage 1A1-IIA cervical cancer at KUH from November 2011-December 2013 were considered eligible for inclusion. The questionnaire used was in Swedish, and an inability to understand the Swedish language the only basis for exclusion. The final study population consisted of 26 patients who all underwent nerve-sparing modified type B Querleu-Morrow surgery (82). (*Figure 9*)



BSO = bilateral salpingo-oophorectomy
**16 less than 45 years of age and included in the AMH analysis*

*Figure 9. Flow chart illustrating the selection of patients for inclusion in **Study III***

4.1.4 Study IV

Between July 2017 and May 2019, women between 18-75 years with presumed FIGO stage IA2-IBI cervical cancer (42) scheduled consecutively for RRH were identified for potential inclusion in this study. The exclusion criteria were inability to understand the Swedish language or coexistence of another malignancy (*Figure 10*). Type C1 Querleu-Morrow RH (82) including complete PLND was performed in all participants.

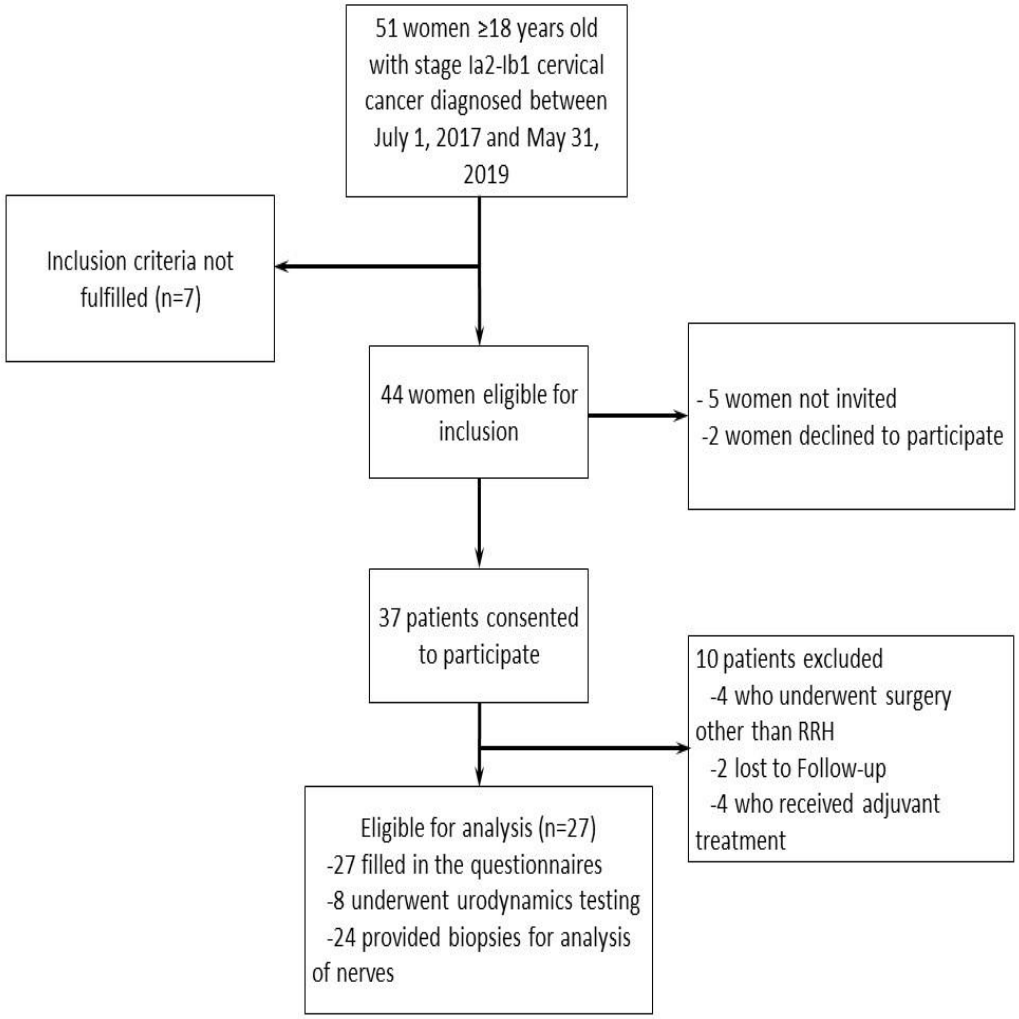


*Figure 10. Flow chart illustrating the selection of patients for inclusion in **Study IV***

4.2 METHODS

4.2.1 Study I

The hospital database for surgery (ORBIT) was used to identify patients who underwent RH during the period 2009-2015. For this purpose, the codes for RH (LCD30, LCD31), robot-assisted surgery (ZXC96) and pelvic lymphadenectomy (PJD55) were combined with the code for cervical cancer (C53.9). ORH was performed by five certified surgical gynecological oncologists. RRH was carried out by three surgeons well experienced in both types of surgery and who had performed RRH $\geq$ 25 times prior to this study.

4.2.1.1 Medical records

Patient and tumor characteristics including the FIGO stage, histology, any adjuvant therapy, operation time, length of hospital stay (LOS), yield of lymph nodes, follow-up time, any need for transfusion, any readmission within 30 days, surgical conversions, recurrences and death were retrieved from medical records. Oncologic safety was assessed on the basis of lymph node metastasis, surgical margins, LVSI, infiltration of the cervical stroma, and requirement for preoperative and/or adjuvant treatment.

4.2.1.2 Surgical complications

To minimize subjective evaluations, complications were graded using the Clavien Dindo (CD) system (*Table 7*), which is based on the intervention required to correct the complication (218, 219). Since complications during the operation are not covered by this system, they were registered separately.

Table 7. Complications according to Clavien Dindo (218)

Degree	Definition
I	Any deviation from the normal postoperative course that does not require intervention or pharmacological treatment
II	A complication requiring pharmacological treatment
III	A complication requiring some other intervention
IIIa	A complication requiring an intervention without general anesthesia
IIIb	A complication requiring an intervention under general anesthesia
IV	A life-threatening complication
IVa	Dysfunction of a single organ
IVb	Dysfunction of multiple organs
V	Death

4.2.1.3 Cost per patient

Most of the regions in Sweden register all patient-related costs according to Cost Per Patient (CPP). This includes ward costs (i.e., for the staff, radiology, laboratory tests, medication) and costs for the operating theater, postoperative care and drugs. Earlier, based on a seven-year depreciation of the value of the robot and an annual performance of 350 operations, Reynisson and Persson estimated the cost of robot-assisted surgery (155). We used their model to calculate the costs related to the robotic procedures which our patients underwent. We also included costs for complications within 30 days after surgery. The Swedish Currency (SEK) was converted to US dollars (USD) using the 2013 currency rate (US $1 = 6.51 SEK).

4.2.2 Study II

In this nationwide population-based cohort study, the participants were identified via the national SQRGC. To ensure the quality and conformity of the data obtained and identify patients not yet registered, the relevant hospital registries were reviewed and validated.

4.2.2.1 The SQRGC

Providing all relevant information to the Swedish National Cancer Registry (NCR) is mandatory for both clinicians and pathologists. The coverage of malignant tumors is greater than 95% and 99% of the diagnoses have been verified histologically (220). However, this registry lacks clinical data regarding treatment and follow-up, which led to the establishment of the SQRGC in 2008, with registration of cervical cancer starting from 2011. Patient consent is obtained for registration. The SQRGC is online and updated prospectively by all hospitals and clinics in Sweden. A manual with definitions and criteria for each variable is easily accessible.

Information on any individual can be accessed using the personal identification number assigned to all residents in Sweden and also linked to both the NCR and the National Causes of Death Registry, enabling coverage, control and life-long follow-up of patients. Comparison of the SQRGC data on ovarian and endometrial cancer with the original medical records demonstrated 70–100% agreement (221).

4.2.2.2 Medical records

Patient and tumor characteristics including size and margins, lymph node yield and status, and any recurrence and complications were extracted from their medical records. In addition, adjuvant therapy administered was registered. Follow-up continued until the time of death or October 24, 2018, whichever came first.

4.2.3 Study III

In connection with their first visit to the outpatient clinic to be scheduled for surgery, the women were asked to participate in this study. Those who agreed answered one validated questionnaire at baseline (prior to surgery) and one year after surgery (*Figure 11*). At these same time-points, a blood sample was taken.

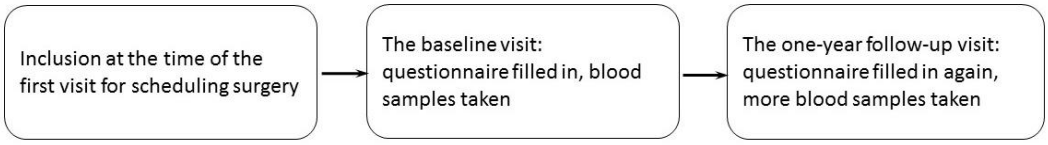


Fig 11 Timeline for Study III

The validated questionnaire used "A study-specific questionnaire developed for women with cervical cancer" covers general well-being (9 questions), sexual function (39 questions), bowel and urinary functions (16 questions each), and lymphatic problems (4 questions). For further information regarding this questionnaire, please see Paper III page 1406 (supplementary S1 and S2).

Blood samples

Blood samples for determination of FSH, LH, SHBG, estradiol, total testosterone, androstenedione and AMH were taken at the same timepoints when the questionnaires were completed. For details concerning the manufacturers, analytical procedures, and limits of detection and CVs (*Table 8*). The level of free testosterone was calculated with the equation of Södergård et al. (222), which is based on the total levels of testosterone and SHBG and an assumed concentration of 40 g albumin per liter blood.

*Table 8. Overview of the assays used in **Study IV***

Hormone	**Procedure**	**Lower limit of detection**	**Intraassay precision (CV)**	**Interassay precision (CV)**
AMH	electrochemiluminescence (ECLIA)	0.13 ng/mL	3.7%	4.4%
FSH	time-resolved fluoroimmunoassay	<0.05 E/L	1.3%	2.6%
LH	time-resolved fluoroimmunoassay	<0.05 E/L	1.8%	2.6%
Androstenedione	liquid chromatography-tandem-mass spectrometry	0.3 nmol/L	5% (intra and inter CV combined)	
Testosterone	liquid chromatography-tandem-mass spectrometry	0.1 nmol/L	6% (intra and inter CV combined)	
Estradiol	Electrochemiluminescence	150 pmol/L	3.0%	4.5%
SHBG	electrochemiluminescence	0.35 nmol/L	1.3%	2.4%

AMH = Anti-Müllerian hormone; FSH = follicle-stimulating hormone; LH = luteinizing hormone; SHBG = sex hormone-binding globuline; CV = coefficient of variation

4.2.4 Study IV

In connection with their visit to the outpatient clinic to schedule surgery, the women were informed about this study. Those who agreed to participate answered two validated questionnaires (ICIQ-LUTSqol and ICIQ-FLUTS) regarding bladder function and quality of life at baseline (prior to surgery) and 2-3 weeks (+/- 3 days), 3 months (+/- 2 weeks) and 12 months (+/- 4 weeks) after surgery (*Figure 12*). At these same time-points, they filled in lists regarding micturition and underwent bladder function tests (urodynamics). At surgery, biopsies were taken from six places along the resection line of the uterus (bilateral at the sacrouterine and vesicouterine ligaments and paracervical tissue), which were stained with S-100 (an antibody that binds to autonomic nerves), and the staining was thereafter quantified.

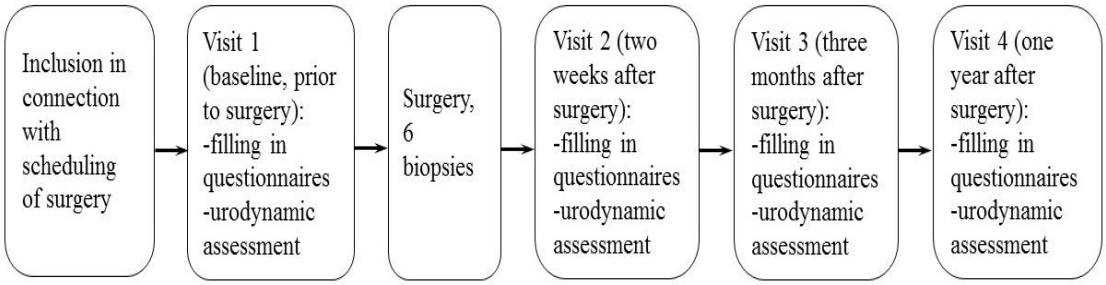


*Figure 12. Timeline **Study IV***

4.2.4.1 Questionnaires

Subjective evaluation of the bladder function was performed employing the Swedish version of the Female Lower Urinary Tract Symptoms (ICIQ-FLUTS) and Quality of Life (ICIQ-LUTSqol) modules of the International Consultation on Incontinence Questionnaire. The validated ICIQ-FLUTS questionnaire consists of 12 questions divided into three domains, where symptoms of filling are rated on a scale of 0-16, voiding symptoms on a scale of 0-12, and symptoms of incontinence from 0-20 (223). In addition, a scale of 0-10 is used to assess the degree of personal distress caused by each symptom.

The 19 items of the validated ICIQ-LUTSqol questionnaire (224) assess the impact of urinary incontinence and other urinary problems on physical and social life, personal relationships, emotions and sleep. All questions are scored as 1-4 (not at all/never, slightly/sometimes,

moderately/often, a lot/all the time), with the three items concerning personal relationships also including “not applicable” as an alternative. The overall final score ranges from 19-76, with higher values indicating a greater impact on QoL. Finally, one last question concerns the extent to which the urinary symptoms interfere with everyday life, with scoring form 0 (not at all) to 10 (maximally). Each of these questionnaires takes about 20 minutes to fill in and they were completed at home.

Clinically minimal important difference (MID) has previously been defined as a change of more than 6 points in the LUTS-qol (225).

4.2.4.2 The VAS scale

In connection with these investigations, the pain experienced by each subject was assessed on the visual analog scale (VAS) commonly used to evaluate subjective pain intensity in clinical trials. The patient indicates the intensity of her pain by placing a mark at the appropriate point on a 100-mm line representing no pain at one end and extreme pain at the other (226).

4.2.4.3 The urodynamic investigations

All procedures were performed while the woman was sitting up straight. The flowmetry and invasive UDS were carried out using the Duet MultiP device (Medtronic Inc., Minneapolis, MN, USA) and air-charged urethral and abdominal sensors. In connection with the invasive procedure one catheter with a pressure sensor was inserted into the bladder and another, in order to determine abdominal pressure, into the rectum. Subtraction of the abdominal pressure from the intravesical pressure gave the pressure generated by the detrusor.

For the performance of cystometry, the bladder was filled (40 ml/min) with saline at body temperature, with recording of any leakage (due either to the increased pressure or poor sphincter function) and of the subsequent time-points at which the first sensation, first desire to void and strong desire to void were experienced. Changes in detrusor pressure, detrusor overactivity and low compliance of the bladder were noted. Thereafter, the patient was allowed to void and the pressure-flow monitored as an indicator of contraction of the detrusor, as well as the resistance of the outlet. As a measure of the strength of bladder contraction, the bladder contractility index (BCI) was determined using the formula pDet@Qmax+5Qmax. Bladder voiding efficiency BVE was taken as an indicator of the effectiveness of bladder emptying (227).

The results of all urodynamic investigations were reviewed for potential errors and inconsistencies by the same experienced urologist.

4.2.4.4 Nerve count

Following surgery, six areas at the resection margin of the uterus (bilateral at the sacro-uterine ligaments, vesico-uterine ligaments and paracervical tissue) were marked and the specimens then transported immediately to the laboratory at the Department of Pathology, where bilateral biopsies were taken from each of the three regions. The longitudinal paracervical tissue was labeled 2 cm lateral to the isthmus of the uterus. The nerve fibers in microscopic sections of the full-length biopsies were stained for the S-100 protein, a general marker for nerves (*Figure 13)* and then counted by an experienced pathologist who was blinded to the clinical information and surgical protocol. The nerves were categorized as small (<100 µm in length) or large (>100 µm) and the area and number of nerves/mm^2 calculated.

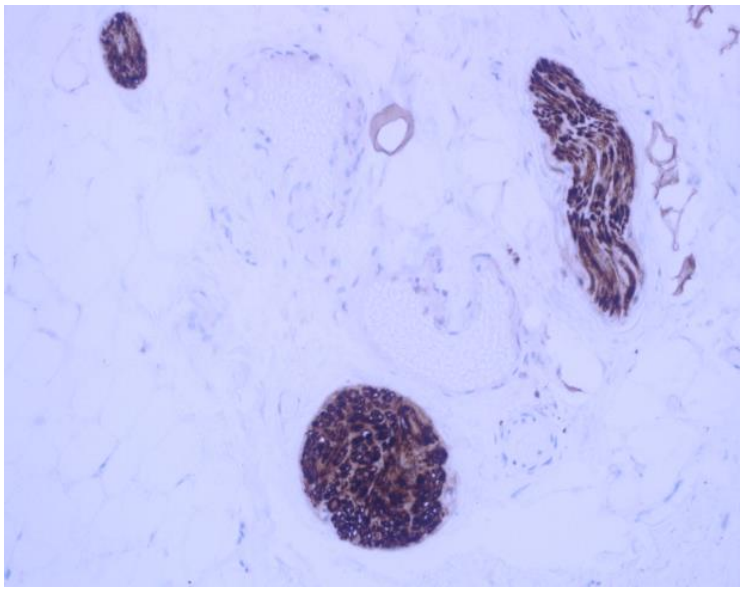


Figure 13. Staining of nerves (longitudinal section at the top left and right and cross-section at the bottom) with S100. Magnification:20X.

4.3 STATISTICAL ANALYSIS

4.3.1 Study I

Student´s t-test was used for comparison of continuous variables and Fisher´s exact test for discrete variables. Risk factors for recurrence were analyzed by Cox regression. In all cases, statistical significance was defined as $p < 0.05$ and statistical analysis performed using the IBM SPSS for Windows software, version 23.0 (IBM Corp., Armonk, NY, USA).

4.3.2 Study II

OS and DFS were examined with Cox and propensity score regression analysis, as well as univariable multivariable regression analysis.

For comparison of continuous variables, student´s t-test was applied, while categorical variables were evaluated using Pearson's chi-squared test or Fisher's exact test, depending on the size of the category.

The Kaplan Meier approach (228) was used to estimate survival. In addition, the proportional hazards model was used to estimate HRs for each of the following variables: age, grade and size of the tumor, lymph-vascular space invasion (LVSI), lymph node status and primary treatment.

The difference in survival following ORH and RRH was estimated using a proportional hazard model (229) with matched data. Potential bias in this estimate was minimized by propensity score matching (230) that took age, grade and size of the tumor, LVSI, lymph node status, primary treatment and year of diagnosis into consideration.

In all cases, the R statistical software, version 3.5.1, was employed for statistical analysis and a p-value less than 0.05 was considered significant. The 'Survival' package, version 2.42.3, was used to estimate survival and proportional hazard and the 'MatchIt' package, version 3.0.2, to match data on the basis of the propensity score

4.3.3 Study III

In light of the small study population and data that were not distributed normally, non-parametric tests were utilized. Changes in symptoms from baseline to the one-year follow-up, as indicated by the answers to the questionnaire, were analyzed and compared employing a sign test. This test reveals differences within a group, with each participant acting as her own control. The values presented are the numbers of women exhibiting improvement, no change

or impairment. Also because of the small study population, a two-sided p-value of <0.01 was considered statistically significant.

The changes in hormone levels from baseline to one year after treatment were analyzed with the Wilcoxons signed-rank test. The groups with or without intact ovarian function were compared using the Mann-Whitney U test.

All statistical analyses were performed in the IBM SPSS for Windows software, versions 22.0 and 23.0 (IBM Corp., Armonk, NY, USA).

4.3.4 Study IV

When relevant, the characteristics of the participants are presented as numbers (n), proportions, and median (range). Normal distribution of the data was confirmed by application of the Shapiro-Wilk´s test. The results of the questionnaires and urodynamic investigations are presented as medians and ranges and comparisons were performed with non-parametric tests. Friedman´s test was used for analysis of the questionnaire data and overall results at the different time-points. The Wilcoxon sign rank test was used to compare the urodynamic parameters at the different time-points, as well as for *post-hoc* evaluation of each participant.

A potential relationship between the numbers of nerve fibers and bladder function was explored by determining Spearman´s correlation coefficient. A P-value of <0.05 was considered statistically significant. All statistical analyses were carried out with the IBM SPSS for Windows software, version 25.0 (IBM Corp., Armonk, NY, USA).

Ethics

All studies were approved by the Regional ethical review boards at Karolinska Institutet, Stockholm in the case of **Studies I, III**, and **IV** and at Gothenburg University for **Study II**.

5 RESULTS

5.1.1 Study I

For patient and tumor characteristics please see *Table 5*. The surgical outcome of RRH was more favorable, with fewer intraoperative complications, shorter hospital stay and less need for blood transfusion, but with no difference with respect to postoperative complications (*Table 9*). In addition, with RRH the lymph node yield was less (22.7% versus 28.9%), as well as the frequency of adjuvant treatment (20.1% versus 29.7%). The LVSI was more commonly found in the hysterectomy specimen after RRH (*Table 10*). The calculated CPP was 116,613 SEK in the case of ORH and 121,861 SEK for RRH (ns).

Table 9. Surgical outcomes following ORH (n=155) and RRH (n=149). The values presented are means ± standard deviations or n (%).

	ORH	**RRH**	p-value
Duration of operation, min	197 ± 46.4	206 ± 44.6	ns
Estimated blood loss, mL	**596** ± 500	**80.9** ± 79.7	<0.0001
Length of hospital stay, days	**6.3** ± 1.6	**2.4** ± 1.8	<0.0001
Lymph node yield	**28.9** ± 13.3	**22.7** ± 9.3	<0.0001
Readmission within 30 days	**2** (1.3)	**18** (12.1)	<0.001
Intraoperative complications	**15** (9.7)	**4** (2.7)	<0.05
CD early I-II	**58** (37.4)	**56** (37.6)	ns
CD late I-II	**6** (3.9)	**11** (7.4)	ns
CD early ≥IIIa	**4** (2.6)	**3** (2)	ns
CD late ≥IIIa	**7** (4.5)	**9** (6.0)	ns

CD= Clavien Dindo (218); early=within 1 month. late= after one month; ns = not statistically significant

Table 10. Oncologic outcomes following ORH (n=155) and RRH (n=149).
The values presented are n (%).

	ORH	**RRH**	p-value
Positive lymph nodes	**22** (14.2)	**13** (8.7)	ns
Lympho-vascular space invasion	**32** (20.6)	**49** (32.5)	<0.05
Adjuvant radio-chemotherapy	**46** (29.7)	**30** (20.1)	0.06
Preoperative brachytherapy	**47** (30.3)	**3** (2.0)	<0.0001
Recurrence	**16** (10.3)	**20** (13.4)	ns
Local	4 (2.6)	8 (5.4)	ns
Loco-regional	2 (1.3)	4 (2.7)	-
Distant	10 (6.5)	8 (5.4)	-

ns = not statistically significant

5.1.1.1 Recurrence and survival

The overall rates of recurrence following ORH and RRH were 10.3% and 13.3%, respectively, with a somewhat higher, although not statistically significant incidence of loco-regional recurrences after RRH (*Table 10*). After adjusting for tumor size and histology, adjuvant therapy and positive lymph nodes, the HR for recurrence following RRH versus ORH was 2.13 (95% CI, 1.06-4.26). (*See Table 5 in Paper I, page 541*). The localizations of the recurrences are documented in *Table 11*.

TABLE 11. Annual numbers, localization and postoperative time-point of recurrence following ORH or RRH for early-stage cervical cancer.

	ORH (total n=16)	**RRH** (total n=20)
Year	N Localization (time-point in postoperative months)	N Localization (time-point in postoperative months)
2006	2 distant (17, 84) 1 local (4)	-
2007	3 distant (2, 15, 18) 2 loco regional (20, 60) 1 local (20)	-
2008	2 distant (6,35)	-
2009	2 distant (52,62)	0
2010	1 local (7)	2 distant (22, 24) 1 loco regional (11)
2011	1 local (10)	2 distant (7,41) 1 local (5)
2012	0	2 distant (5, 10) 3 loco regional (7, 17 31) 4 local (3, 5, 12,17)
2013	0	2 distant (3, 9) 1 local (23)
2014	1 distant (15)	2 local (6, 10)
2015	0	0

A Kaplan-Meier plot (not published elsewhere) revealed a significant difference in PFS in favor of ORH (82.5% versus 90.7%, log rank p<0.05) (*Figure 14a*). The OS for the two groups did not differ significantly (92.7% versus 91.1%, log rank 0.87) (*Figure 14b*).

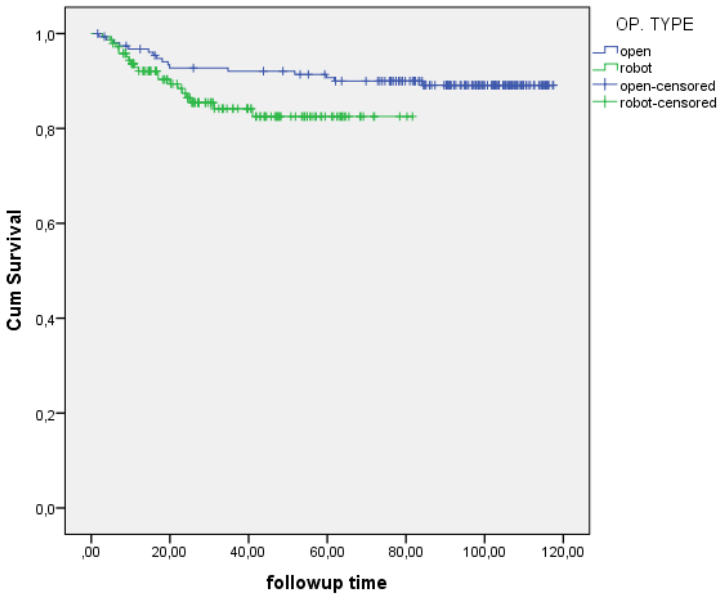


Figure 14a. Progression free survival (PFS) for women treated for early cervical cancer by radical hysterectomy with an estimated 5-year PFS of 90.7% in the open surgical cohort versus 82.5% in the robot-assisted surgical cohort, log rank p<0.05.

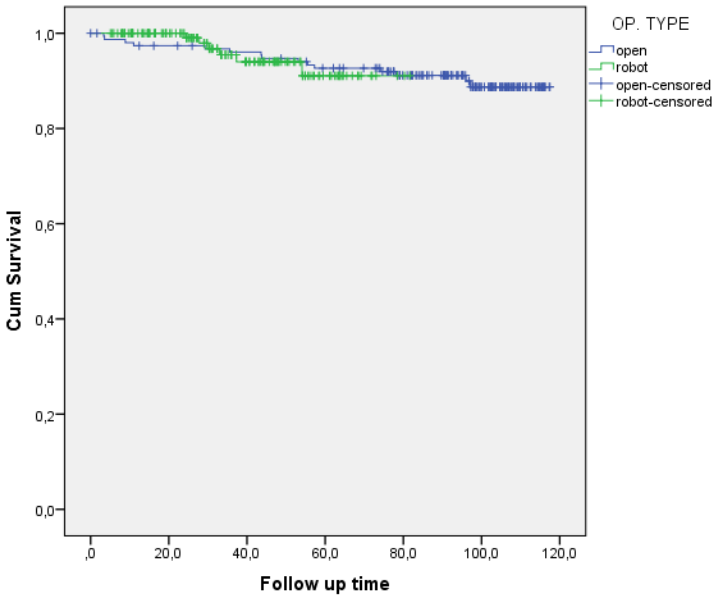


Figure 14b. Overall survival (OS) for women treated for early cervical cancer by radical hysterectomy with an estimated 5-year OS of 91.1% in the open surgical cohort versus 92.7% in the robot-assisted surgical cohort, log rank 0.87.

5.1.2 Study II

Of the 864 women included, 236 (27%) underwent ORH and 628 (73%) RRH. After propensity score matching, no differences between these groups with respect to age, BMI, or FIGO stage, histology or grade of their tumours were observed. The lymph node yields with ORH and RRH were 26 and 23, respectively ($p<0.01$), with a similar number of lymph nodes metastases in both cases. Following ORH, 32.2% received adjuvant therapy compared to 20.9% after RRH ($p<0.05$) and the corresponding follow-up times was 55.7 and 44.5 months ($p<0.001$) (*Table 5*).

5.1.2.1 Recurrence of disease

In total, 84 (9.7%) of the patients suffered from recurrence of their cervical cancer, with no difference in this respect between the groups (n=0.12). Vaginal metastasis were more frequent after RRH (29 (35.8%) versus 13 (27.7%)), with no differences in locoregional (pelvic wall) metastasis (22 (27.2%) versus 12 (25.5%), respectively) or abdominal and distant metastasis. There were 7 port-site metastases following RRH.

5.1.2.2 Survival

The 5-year DFS following ORH or RRH was 84% (CI 95%, 79-90) and 88% (CI 95%, 85-91), respectively. After adjusting for tumour size or stratifying into surgery alone or in combination with adjuvant therapy, this value for the two groups did not differ. No statistical difference was found regarding the 5-year OS; 92% (CI 95%, 88-91) for the open and 94% (CI 95%, 91-96) for the robotic group respectively. After adjusting for tumour size or stratifying into surgery alone or in combination with adjuvant therapy, these values for the two groups did not differ. (*Figure 3 in Paper II, page 175*)

Although the univariable analysis of OS as the end-point indicated that the grade and size of the tumour, LVSI, lymph node status and adjuvant therapy were all associated with poorer prognosis, the multivariable analysis did not indicate any such association. With DFS as the end-point, univariable analysis indicated that these same factors were associated with an increased risk of recurrence, but according to the multivariate analysis only tumour size ($p>0.001$) and grade 3 ($p=0.02$) were independent risk factors in this respect. (*Table 2 in Paper II, page 175*)

5.1.3 Study III

Of the 26 women eligible for analysis, 85% were premenopausal (as defined by serum levels of FSH at baseline). Twenty-one women with preserved ovaries were included in the hormone analysis and 16 among them who were below 45 years of age were also analysed for AMH *(Table 6 and Figure 9).*

5.1.3.1 Functional outcomes

One-year after undergoing RRH, 62-64% of the women experienced attenuated anxiety and depression ($p<0.01$). No significant change in sexual function, i.e., no increase in problems with desire, arousal and orgasm. More than 90% were sexually active one year after treatment. However, a tendency towards sexual distress, with more labial numbness ($p=0.04$) and deep pain during intercourse ($p=0.02$), was reported.

32-35% of the women experienced deteriorated bladder function, i.e., urinary retention and the need to strain to initiate urination (*Table 12*). No problems with urinary tract infections, urgency or incontinence were reported. No symptoms involving the bowel, such as urgency to defecate, pain when defecating, or increased stool leakage were reported. However, lymphedema was also a significant problem one year after surgery.

Table 12. Bladder function and lymphatic problems one year after RRH (n=26).

Variable	Deterioration relative to baseline (%)	p-value
Incomplete bladder evacuation	32	0.04
Straining to initiate micturition	35	<0.01
Swelling of the legs and lower abdomen	46	<0.01
Heaviness in the legs and lower abdomen	35	<0.01

5.1.3.2 Levels of sex steroid hormones

One year after RRH serum levels of FSH and LH in women with preserved ovaries were elevated ($p<0.01$ respectively) while no significant alterations in the levels of testosterone, SHBG, estrogen or androstendione were observed. In women < 45 years of age the level of AMH had decreased from an interquartile range of 0.35-1.85 ng/mL to 0.18-1.33 ng/mL ($p = 0.02$).

5.1.4 Study IV

Twenty-seven women, median age 43, were eligible for analysis. For patient and tumor characteristics please see *Table 6*. One complication >grade II, according to CD (218), was reported (i.e., a deep abscess in need of drainage).

5.1.4.1 The FLUTS and LUTSqol questionnaires

The women started with a score of 19 for the LUTSqol, indicating that they experienced few symptoms that affected their quality of life prior to surgery. At the first visit two weeks after surgery, this score had increased to 27 ($p<0.05$). Three months after surgery the score was almost normalized, but one year after treatment the LUTSqol score was again significantly higher than at baseline (median score 25 ($p<0.05$)).

The FLUTS score demonstrated the same pattern. Two weeks after surgery, the scores for filling and voiding encompassed were significantly elevated ($p<0.05$), as well all scores three months after surgery ($p<0.05$). The symptoms connected with filling and voiding, as well as incontinence had improved one year after surgery, but were still increased ($p<0.05$). (*Table 13).* Altogether, less than 25% of the subjects still experienced bladder dysfunction one year after surgery.

Table 13. Scores (medians and ranges) of the questionnaires concerning subjective distress caused by the post-operative complications and its impact on quality of life (QoL) at the different time-points after surgery.

Outcome variable	Baseline	2 weeks	3 months	1 year	p[c]
QoL[a]	19 (16-30)[2,3,4]	27 (16-58)[1]	20 (17-53)[1]	25 (17-47)[1]	0.004
Total distress caused by the symptoms[a]	0 (0-5)[2,3]	3 (0-10)[1]	0.5 (0-9)[1]	0 (0-8)	0.006
Problems with[b]					
Filling	1 (0-8)[2,3,4]	3 (0-10)[1,3]	2 (0-10)[1,2]	2 (0-10)[1]	0.002
Voiding	0 (0-6)[2,3,4]	4 (0-10)[1,3,4]	3 (0-11)[1,2]	2 (0-9)[1,2]	<0.001
Incontinence	0 (0-5)[3,4]	2 (0-10)	2 (0-11)[1]	1 (0-8)[1]	0.002

[a] as determined by ICIQ-LUTSqol

[b] as determined by ICIQ-FLUTS

[c] p value assessed with the Friedman´s test for overall results at the different time-points

Statistically significant differences ($p<0.05$) between the different time-points were examined for with the Wilcoxon sign rank test:

[1] significantly different from the corresponding value at baseline

[2] significantly different from the corresponding value at two weeks

[3] significantly different from the corresponding value at three months

[4] significantly different from the corresponding value at one year

5.1.4.2 Urodynamics

The uroflowmetry and pressure-flowmetry indicated a hypotonic bladder with a tendency (although not statistically significant) towards increased capacity and voided volume. Moreover, the mean maximal flow rate (MFR) in connection with spontaneous micturition tended to be slower two weeks after surgery, suggesting that the contractility of the bladder was reduced. There was a tendency towards delayed sensations, as well as increased cystometric capacity during the entire follow-up period.

The pressure-flowmetry showed an impairment in the maximal detrusor pressure associated with micturition after surgery that remained throughout the study period ($p<0.05$). This procedure also revealed a significant increase in the residual volume after one year. At the 12-month follow-up, one woman had developed detrusor overactivity and another leakage of urine. (*Figure 15 and Table 14)*

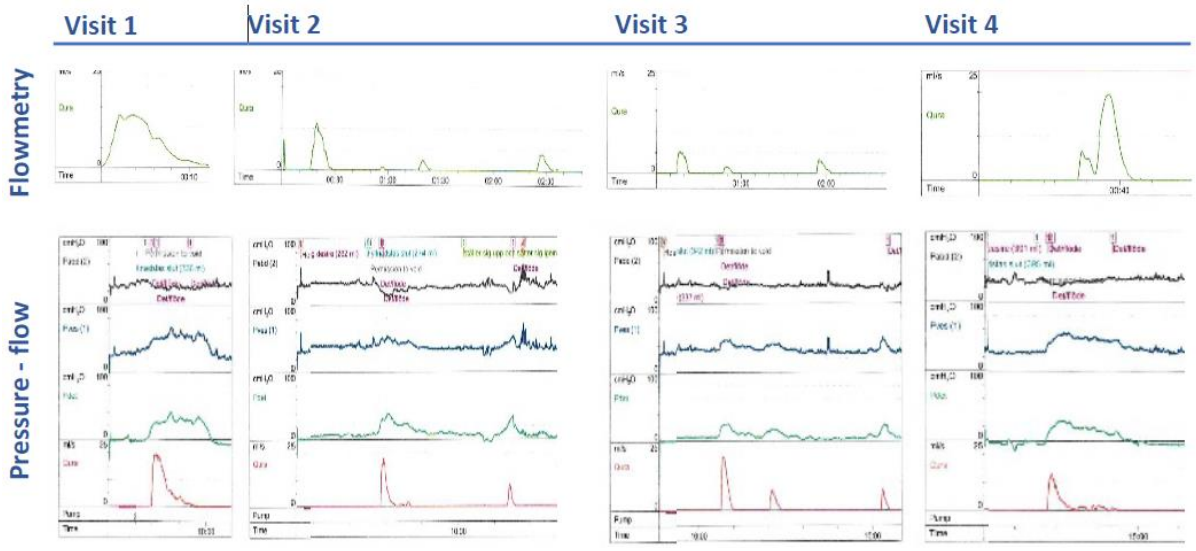


Figure 15. Flowmetry and pressure-flow curves for one patient in connection with all four visits. In connection with visit 1, flowmetry and pressure-flow were normal. At the time of visit 2, the flowmetry revealed fractionated voiding and the pressure-flow study indicated that detrusor contraction was diminished in both strength and duration. This same pattern was apparent at visit 3. By visit 4, one year post-surgery, the strength and duration of detrusor contraction had improved.

Table 14. Urodynamic characterization of the women who underwent RRH prior to and at various time-points after the operation. The values presented are medians (ranges).

	Before RH	**2 weeks after RH**	**3 months after RH**	**1 year after RH**
N	8	5	6	7
VAS	0 (0-3)[2,3]	2 (0-4)[1,3]	0 (0-6)[1,2]	0 (0-5)
Uroflowmetry				
Voided volume (ml)	92 (26-511)	96 (17-251)	148.5 (64-189)	227 (11-538)
MFR (Qmax in ml/s)	21.3 (4.2-24.8)	11 (5.9-35.1)[4]	24.4 (5-27.6)	26.6 (1.8-43.1)[2]
	n (%)	n (%)	n (%)	n (%)
PRV (ml)	4.4 (0-34)	0 (0-8)	15 (0-40)	5 (0-45)
Cystometry (ml)				
First sensation	203 (77-248)	202 (65-296)	213 (86-698)	244 (103-322)
First desire to void	278 (150-337)[3]	304 (178-351)	295 (206-699)[1]	309 (190-562)
Strong desire to void	362 (232-676)	381 (262-588)	399 (337-700)	500 (210-578)
Cystometric capacity	366.5 (248-677)	386 (274-597)	404 (340-700)	511 (395-597)
Pressure-flow				
Voided volume (ml)	356 (249-617)	450 (225-537)	499 (335-700)	537 (239-587)
Maximal detrusor pressure	28 (22-47)[2,3,4]	12.5 (5-40)[1]	20 (5-38)[1]	17 (2-26)[1]
MFR (ml/sec)	21 (10.9-26.4)	24.9 (17-28.6)	20.4 (10-35.7)	18.6 (12-25.1)
PRV (ml)	6.5 (0-199)[4]	49.5 (0-123)	9 (0-128)	144 (0-250)[1]
BCI	130 (84.5-159)[4]	140.5 (95-169)	131 (60-185.5)	112.5 (62-143)[1]
BVE	97 (56-100)[4]	87.8 (80.8-100)	98 (80-100)	80 (46.6-100)[1]

VAS=Visual Analog Scale, MFR=Maximal flow rate; PRV=Postvoid residual volume (ml); BCI=Bladder contractility index; BVE=Bladder voiding efficiency

Statistical significance ($p<0.05$) was assessed with the Wilcoxon sign rank test
[1] significantly different from the corresponding value at baseline
[2] significantly different from the corresponding value at two weeks
[3] significantly different from the corresponding value at three months
[4] significantly different from the corresponding value at one year

6 DISCUSSION

In contrast to the introduction of new pharmacological treatments, implementation of novel surgical modalities is never preceded by safety studies. The inherent nature of surgical treatment, where the operator proficiency is paramount, necessitates a gradual assessment of novel technologies. Robot-assisted laparoscopy is no exception and the development has been driven by individual surgeons and perceived benefits often exaggerated. In addition, marketing strategies by the industry have a major impact. RCTs constitute post-hoc evidence and the relevance for procedural interventions has been questioned. Finally, cost consciousness is essential to ensure acceptance of novel treatment modalities.

The overall aim of the current project was to establish the oncologic safety and to assess long-term functional outcomes of RRH for the surgical treatment of early stage cervical cancer. To assess the oncologic and surgical outcomes after RRH, we performed two population-based cohort studies (**Study I** and **II**). In our regional analysis (Study I), RRH was associated with an increased risk of recurrence whereas the nationwide study (Study II) showed no difference between RRH and ORH. Similar postoperative morbidity and health care costs were observed in Study I but intraoperative adverse events were less by RRH.

In **Study III** and **IV**, only minor effects on sexual function were reported, but bladder dysfunction and lymphedema remained significant consequences after RRH. The cause of functional impairment after RRH cannot be explained by nerve ablation alone and should be further investigated. Prospective trials concerning the oncologic safety of RRH are needed.

6.1 STUDIES I AND II

Before the publication of the LACC-trial in 2018, a number of observational studies demonstrated reassuring oncologic safety of MIS/RRH compared to ORH (102, 107, 116, 118, 123-125). Study I presented in this thesis was one of the first retrospective analysis to suggest inferior survival after RRH. Certainly, publication bias is a well-known phenomenon after negative study outcomes and is likely more frequent when expensive technology is evaluated (134). After the LACC-trial was published, inferior oncologic outcome after MIS has been reported repeatedly (129-133, 231-234). In this perspective, the results from our nationwide study stand out with no observed survival differences between RRH and ORH. Similar data has recently been reported from Denmark and the two studies together comprise close to 2000 women from similar settings (235). In contrast to most participating countries in the LACC-trial, Swedish and Danish cancer care is highly centralized and treatment principles adhere to national guidelines. In addition, very few women underwent conventional laparoscopy and

reporting to national quality registries is mandatory in both countries. Although observational studies typically are considered hypothesis generating, it could be argued that large population-based studies reflect "real world data". However, data from the SQRGC was restricted to 2011-2017 and earlier data was not available in the analysis. Indeed, the discrepancy between the oncologic outcome in the population-based **Studies I** and **II** is probably explained by selection bias, as the data source in the regional study included all procedures from 2009 and onwards. In Study I, almost twice the recurrence rate was observed in the first 50 RRH compared to last 50. Taken together, our data from the observational studies suggest that RRH is non-inferior to ORH if the initial learning-curve is omitted. Methodological differences between the Scandinavian studies precludes direct comparisons and a "hidden" learning-curve cannot be ruled out in the Danish study. Adoption of novel techniques is always accompanied by an initial learning phase before a plateau, representing proficiency, is reached. However, the impact of surgical training has typically focused on perioperative outcomes including operative time, blood loss and complications (236). The results from Study I and II are supported by a recent single-center study from the Netherlands where the authors observed an institutional learning-curve of at least 61 cases before an initial harm of RRH was neutralized (237). Preliminary data on the RRH learning-curve from Sweden suggest that in addition to a higher recurrence rate, a different pattern with more advanced, abdominal recurrences occurred in the early phase (unpublished data). Moreover, a retrospective analysis of laparoscopic radical prostatectomy indicated that the risk for recurrence within 5 years was approximately 10% higher if the operation was performed by surgeons with the least experience (238). Although no such comparison regarding RRH has been performed, mortality appears to be higher if the gynecological surgeon performs less than 12 procedures annually (239).

The assessment of operator competency in RCTs for procedural interventions is clearly of utmost importance to avoid type II errors. In the LACC-trial, proficiency was subjectively evaluated through analysis of videos submitted by participating surgeons. However, the LACC-trial was initiated in 2008 when few surgeons had gained sufficient experience from minimally invasive radical hysterectomy. RH by conventional laparoscopy is generally considered to be one of the most demanding surgical procedures in gynecologic oncology and considering the rarity of early stage cervical cancer in most developed countries, the learning-curve ought to be substantial. The observed clustering of recurrences to 14 of the 33 participating centers in the LACC-trial reinforces the impression that surgical proficiency was inadequate in many institutions.

Other potential causes for inferior survival after MIS have been discussed extensively. Preclinical studies have suggested that the CO_2-gas used to create pneumoperitoneum during MIS may promote the implantation of cancer cells in the peritoneum (240-242). However, this has not been confirmed in humans. Further, the final step of the RH by MIS typically includes intracorporeal colpotomy with exposure of the cervix in the pelvis, which may increase the risk of recurrence (243, 244). Köhler and co-workers recently reported data using a hybrid technique where the vagina was closed prior to laparoscopic RH with survival outcomes comparable with those from the open arm in the LACC-trial (245).

Intrauterine manipulators are widely used to position the uterus during surgery and the use has been proposed to exert an impact on oncologic outcomes (246, 247). A recent retrospective multicenter analysis from Europe included 693 women that underwent RH 2013-2014 and demonstrated an increased risk of recurrence in the MIS group (HR, 2.76; Cl 1.75-4.33) when a uterine manipulator was used (248). Consequently, the use of intrauterine manipulators during MIS for cervical cancer is discouraged but has never been part of RRH in Scandinavia.

In contrast to most previous studies (152-154) no difference in health care costs was observed between RRH and ORH in Study I. This is in agreement with a previous study from Lund where cost neutrality was reached after 90 cases (155). Study I also demonstrated the benefits from the robotic technique including shorter hospital stay, less blood loss and better perioperative outcomes in line with previous research (65, 101, 107, 110, 115-122). Indeed, less intraoperative adverse events were observed after RRH in Study I, suggesting that the superior precision of robot-assisted surgery facilitates complex dissection in high-volume settings. On the other hand, vaginal cuff dehiscence with a partial or complete disruption, occurred in five women. This complication is more common after RRH, probably due to the more extensive use of electrocoagulation and/or inappropriate suturing technique (249).

With the increased awareness of the potentially harmful effects of MIS, the lack of apparent benefits in terms of improved QoL and perioperative morbidity reported from the LACC-trial is of particular concern (135, 179). Robot-assisted laparoscopy is generally considered the most expensive surgical modality and clear benefits should be expected. Two RCTs constitute the basis for the current recommendation to treat endometrial cancer by MIS since both demonstrated superior outcomes after MIS (97, 98). Differences in patient characteristics between the diseases may account for the absence of benefits observed in the LACC-trial with younger and less obese women treated for cervical cancer. However, the negative secondary outcomes in the LACC-trial may reflect inadequate proficiency and “true” effects of MIS on adverse events went unnoticed.

In summary, Study I and II suggest that RRH is safe for the management of early stage cervical cancer once the surgeons have reached adequate proficiency. Awareness of the learning-curve for any new treatment modality is critical and future trials should carefully address this aspect. Cost-effectiveness of RRH can be achieved, especially in countries with centralized cancer care. Future trials need to demonstrate substantial benefits of MIS to justify the continued use of the technology. The continuous development of the robotic platform will hopefully incorporate novel technologies that facilitates surgery and improves survival.

6.2 STUDIES III AND IV

6.2.1 Psychological quality of life

Findings regarding psychosocial well-being after treatment for cervical cancer treatment vary considerably due to differences in the questionnaires employed, follow-up times, patient groups and modes of treatment (167, 168). In **Study III** we evaluated different aspects of QoL with a questionnaire that had been subjected to careful clinimetric validation specifically with regards to patients with cervical cancer (165, 166).

In patients with early-stage cervical cancer, no significant effect of RRH were found on physical or psychological well-being, vitality, feeling of femininity, other's perception of their femininity, self-image, or satisfaction with sexual function. This lack of significant effects could be due to the small number of patients and/or the fact that these aspects of QoL may be of lesser importance and easier to cope with than anxiety and depression.

The increases of 62% and 65% in the levels of anxiety and depression, respectively, observed one year after RRH are in agreement with several other reports on cancer survivors (170, 250). Furthermore, the mental fatigue often reported by survivors after treatment for cervical cancer is an important cause of increased sick leave and loss of work several years later (251). Moreover, most of our subjects were premenopausal and fear of becoming infertile may have exacerbated their anxiety and depression.

A diagnosis of cancer can lead to stress in any relationship. Survivors of cervical cancer are at increased risk of divorce (173) with associated implications for psychosocial well-being. In **Study III**, 92% of the women were involved in a steady relationship prior to surgery, but only 81% had a partner one year after treatment.

6.2.2 Functional outcomes after RRH

With surgical treatment the goal is to maximize the oncologic outcome while minimizing impairment of the patient´s QoL. Although the improved visibility and precision offered by RRH is believed to help spare nerves, many patients who undergo this type of surgery still experience sexual and bladder dysfunction, as well as lymphatic edema, with significantly impaired psychological well-being and HR-QoL. We propose that an explanation for these problems is damage to autonomic nerves in the pelvis, in combination with vaginal fibrosis and PLND. However, other factors, including an altered anatomy, reduced vaginal blood flow, inflammation and postoperative pain may also play a role.

Bladder dysfunction remains one of the predominant side-effects following RH, regardless of surgical approach, as confirmed in **Studies III** and **IV**, where many of our patients still suffered of such dysfunction one year after surgery. Urological morbidity may affect daily QoL (204). Unfortunately, urinary dysfunction may go untreated simply because women are too embarrassed to report this condition spontaneously to their physician (252). Moreover, in connection with follow-up after surgery for cervical cancer, the primary focus is on the efficacy of the treatment and complications are not always dealt with adequately. To deal with this potential reduction in QoL due to bladder dysfunction it is essential both to inform women prior to RH that difficulties in voiding are common afterwards, as well as to take this potential complication into consideration during follow-up. dysfunction (253, 254).

In **Study IV** we found that as determined with the LUTS, QoL was lowered two weeks after surgery, then almost normalized 3 months post-operatively, but had deteriorated significantly again at the time of the one-year follow-up. Interestingly, the score for symptoms was most pronounced two weeks after surgery and thereafter gradually improved, although never returning to the pre-operative status. However, there was no statistically significant correlation between the scores for symptoms and QoL.

In particular, the improvement in LUTSqol observed 3 months post-operatively was not associated with a decrease in symptoms related to filling, voiding and incontinence (as indicated by the FLUTS score). At the one-year follow-up, LUTSqol had declined, even though there was no change in symptoms. At least in part, this might reflect the fact that although the women were pleased that their symptoms had subsided at three months compared to after two weeks postoperatively, after one year with no further reduction in symptoms they had difficulties coping with the possibility of no further improvement. It is also worth noting that

some patients experienced several symptoms that exerted very little effect on their QoL, perhaps due to better coping strategies.

In many examinations, the pressure-flow examination revealed that the bladder had become hypotonic after RRH. For many of the women contraction of their detrusor was weakened one year after surgery, but in connection with the free flowmetry, they could compensate for this by straining or simply relaxing their pelvic floor, thereby still attaining high maximal flow rates. Therefore, the bladder contractility index (BCI) turned out not to be useful in our study, since this parameter is dependent primarily on the maximal flow rate and not on the strength of detrusor contraction.

In addition, we noted that leakage became more common one year after surgery. This observation may reflect a hypo-contractile bladder due to weakening of the pelvic floor as a result of the straining to void.

We found no correlation between the number of autonomic nerves ablated and bladder dysfunction. This does not exclude the possibility that nerve damage has some bearing on bladder dysfunction but indicates that other factors may be of greater importance. In **Study IV,** the acceptable residual volumes for some of the women in connection with catheter extraction 5 days postoperatively were surprisingly large, which might also have influenced bladder function later on. Prolonged catheterization and increased awareness of residual urinary volume may prevent impairment of the detrusor musculature. In addition, compensatory straining at voiding may exaggerate bladder dysfunction and increase the risk of subsequent incontinence.

Finally, the cause of postoperative bladder dysfunction appears to be multifactorial and a combination of preventive measures and raised awareness of early symptoms may reduce the functional consequences of RH for early stage cervical cancer. It is essential in the postoperative phase to avoid bladder overdistention, since damage to the muscle results in fibrosis and weakness in the contraction of the muscle. In addition, the patient should be instructed to refrain from straining since there is a risk of development of urine incontinence (84).

The findings of studies regarding *sexual function* in survivors of cervical cancer are contradictory, observing no deterioration (255) or impairment and associated lowering of QoL (184). However, longitudinal follow-up does reveal problems in this respect after treatment. Jensen and colleagues described that following RRH for earl-stage cervical cancer, women reported significant vaginal problems such as dyspareunia for as long as three months

afterwards, as well as a negative impact on sexual interest and lubrication for up to two years (181).

Several studies on nerve sparing RH have shown an improvement in outcome regarding sexual function (256-258). In our studies RRH exerted less impact on sexual function than has previously been reported following ORH (88, 166, 181, 259). The only symptoms of sexual distress experienced one year after RRH in **Study III** were numbness of the labia and deep dyspareunia. The labial numbness may have resulted from damage to branches of the genitofemoral nerve that occurred during the PLND, whereas shortening of the vagina and fibrosis may lead to deep pain upon vaginal penetration during intercourse. Many of the women reported a feeling of a short vagina.

In previous studies (88, 166, 187, 258) impaired arousal and orgasm were observed following ORH, probably due to surgical trauma to autonomic nerves, with subsequent reductions in vaginal blood flow and lubrication. Except for less satisfactory orgasms ($P = 0.03$), which may be explained by dyspareunia, we found no changes in arousal or the capacity for orgasm one year after RRH. Therefore, we propose that RRH may facilitate preservation of nerves that play an important role in sexual function.

Following ORH, symptoms of *bowel dysfunction* such as constipation, flatus and fecal incontinence have been reported (204, 205). Interestingly, none of these problems was reported by the women involved in **Study III.** We hypothesize that the type B RRH utilized (82), for lateral and posterior dissection of the parametria in this study explains this difference. More extensive dissection may result in increased bowel dysfunction.

Lymphedema is common after PLND (18%-40%), due to disruption of the routes for lymphatic drainage (137, 138). This symptom can be disabling, lowering QoL and, unlike other functional problems worsens with time (169, 170, 260). In our case 46% of the women reported more swelling of the legs and/or abdomen one year after RRH with PLND **(Study III).** It might be possible to reduce the frequency of lymphedema by employing the SNL technique instead of complete lymphadenectomy.

In **Study III** we found elevated serum levels of FSH and LH ($p<0.01$) and a decline in the serum levels of estradiol (ns) in premenopausal women following RRH with preservation of the ovaries. This suggests an adverse effect on the blood supply to the ovaries. Approximately one-third of the ovarian blood supply comes from the uterine artery, which is closed by diathermy during the operation. However, serum levels of FSH and estradiol vary during the

menstrual cycle and since blood samples were not taken standardized according to the menstrual cycle, these findings should be interpreted with caution.

Moreover, we observed a significant lowering of median serum levels of AMH one year after RRH (by 0.26 ng/mL) versus an annual average decrease of 0.16 ng/ml in the general population of fertile women (210) which suggests an effect on the ovarian reserve. This result is in agreement with findings following ORH (211). This decline increases the risk of an early menopause, which may go unnoticed since women lose their period following RH.

Androgens and, in particular, testosterone play a role in sexual function and symptoms of testosterone deficiency can clearly be ameliorated by testosterone replacement (261). However, at present very little is known about ovarian production of androgens following RH. Hallqvist found no association between levels of androgen and sexual dysfunction among women who survived cervical cancer (214). Nor did we find any reduction in the serum levels of either total or free testosterone or androstenedione following RRH with preservation of the ovaries. At the same time, even though we employed a highly sensitive assay for testosterone, small changes in the level of this hormone may have gone undetected.

7 METHODOLOGICAL CONSIDERATIONS

The methodological considerations regarding the prospective follow-up and population-based studies differ. In the two population-based registry studies we tried to adjust for known confounders by applying cox regression, but this assumes that the influence of the predictors on survival remains constant, at least during the study period, which is not the clinical reality. During both **Studies I** and **II** the management of early stage cervical cancer changed and thus introduced a time trend bias. As more experience was gained at KUH, RRH gradually became more radical (type C1 instead of type B). Furthermore, the increased usage of preoperative MRI allowed detection of suspected lymph node metastases, which may have led to increased use of primary radio-chemotherapy treatment.

Enrollment of the patients in clinical trials, as in **Studies III** and **IV,** is challenging. The questionnaires may be perceived as too intimate to answer. In addition, urodynamic examinations can be uncomfortable and sometimes difficult to motivate. Subjective assessment by questionnaires is also influenced by the mood of the patient, which may be poor immediately after she has been diagnosed and is still experiencing symptoms from the cancer. Psychological and social factors may also be interdependent with the measured functional outcomes.

7.1 SELECTION BIAS

A selection bias was apparent between **study I and II.** Since the SQRGC started in 2011 and did not include the first period of RRH in Sweden (performed 2005-2010), the initial learning curve was not included in **Study II**. Limited access to robotic systems in certain regions could have resulted in performance of ORH instead of RRH and introduced a selection bias. Further, in centers with both surgical techniques women with less advanced tumors may have been allocated for RRH. This is supported by the finding of significantly larger tumors in the ORH group in **Study II**. Further, in centers using SLN a selection bias was introduced since women with occult lymph node metastases detected intraoperatively were excluded from RRH. Therefore, more advanced stages were included in the ORH group.

Study III enrolled 26 women out of the 64 who underwent RRH during the study period. Potentially, the answers to the questionnaire by those not included might have been different. This same limitation is associated with **Study IV,** where 44 women were eligible for inclusion, but only 27 answered the two questionnaires. It is possible, although unlikely that the outcome after surgery would have been different in the women not included. There are several reasons for the low number of participants included in **Study III and IV**. Women were not invited to

participate, they declined, or they were lost to follow up. In addition, we excluded women who did not understand Swedish, which might also have introduced a selection bias.

7.2 INFORMATION BIAS

The use of high-quality registries in **Study I** and **II** reduced the risk of information bias. The database for surgery (ORBIT) at KUH includes all women undergoing surgery. The SQRGC, with high coverage, is linked to the NCR, with a coverage of approximately 95% (155). In addition, we reviewed local hospital registries and patient records manually to document recurrence. SQRGC data on ovarian and endometrial cancer have been validated with high agreement to medical records (221). Due to the retrospective nature of **Study I** complications treated in other hospitals could have been missed.

Women who were asked to participate in **Studies III** and **IV** may have been influenced to respond to the questionnaires in a way that focused on symptoms that they would otherwise have ignored, thus reporting more problems related to sexual health, bladder function and/or bowel distress.

In **Study III** for practical reasons the blood samples were neither taken at a specific time nor at a specific menstrual cycle day which could have influenced the results (262, 263). However, serum levels of AMH vary little over the menstrual cycle (264), whereas both the diurnal and menstrual variations in serum levels of testosterone are quite large (263, 265).

An additional potential information bias in **Study III** involved asking the women to answer the questionnaires prior to treatment for their cervical cancer, when they were distressed in a manner that could have influenced their responses. Also, by asking questions retrospectively as in this study at baseline, there is always a risk of recall bias.

7.3 CONFOUNDERS

In **Studies I** and **II** the accurate data obtained from the registries used (NCR; Orbit, SQRGC) allowed adjustment for several confounders. However, other potentially relevant confounders e.g., socioeconomic status, smoking, surgical skills were not possible to adjust for. Nevertheless, in Scandinavia we have a public health care system where socioeconomical status may not influence the provided treatment to the same extent. In the United States women who are white and have private health insurance, a higher income and more education are more likely to undergo MIS (2).

Many factors can influence sexual function, including lifestyle, medical health, cultural and religious beliefs (217, 266). In **Studies III** and **IV**, with a limited sample size, adjustment for such confounders was not possible.

7.4 QOL ASSESSMENT

Patient-reported outcomes are routinely assessed in clinical trials along with more traditional oncologic outcomes. A statistically significant difference of a measured patient reported outcome does not mean that the differences is of clinical importance to the patient. Another problem regarding patient-reported outcome is the interpretation of a change in the score. Does an improvement from 6 points to 3 mean the same as from 9 points to 6? For the questionnaire to be clinically useful the outcome measures need to have adequate validity and ability to detect changes following the intervention (responsiveness). To address this issue a clinical "minimal important difference" (MID) has been introduced to detect changes of clinical importance. For the LUTS questionnaire used in **Study IV** the clinical MID has been described as a change of more than 6 points in the LUTS-qol (225).

7.5 EXTERNAL VALIDITY

External validity concerns reproducibility and the extent to which our findings are also applicable to other conditions, patient-groups and/or other countries. The results from the population-based **studies I** and **II** could be applicable to women in other countries with similar standards of living and health care system.

7.6 PRECISION

In the population-based **Studies I** and **II**, the large size of the cohorts enhances the precision. In **Study IV** we did not show a correlation between the extent of nerve damage and bladder function. Further, in **Study III** we found no decline in serum levels of testosterone, SHBG or androstenedione and only minor sexual dysfunction. In these examples, a type II error may have been present due to the relatively limited size of the study participants and consequent lack of power.

8 CONCLUSION

- The data from the observational studies suggest that RRH has similar oncologic outcomes compared to ORH once the surgical proficiency has been established.

- RRH for early stage cervical cancer has similar costs and postoperative complication rates, but shorter hospital stay and less perioperative advers events compared to ORH.

- RRH appears to have only minor effects on sexual function, but bladder dysfunction and lymphedema remain a significant consequence of RRH which may impact QoL.

- The cause of bladder function after RRH is multifactorial and cannot be explained by nerve ablation alone. Other factors may be of importance and should be further investigated.

- Anxiety and depression were reported to a greater extent one year after surgery for early stage cervical cancer.

- The hormone analyzes after RRH with ovarian preservation in premenopausal women suggest an impaired ovarian function.

9 FUTURE PERSPECTIVES

- Prospective trials need to ensure the safety of RRH and establish the benefits of the robotic technique

- Awareness of the learning-curve for any new treatment modality is critical and future trials should carefully address this aspect.

- Optimal balance between maximal curative outcome and minimal functional morbidity must be established for RH.

- The sentinel node technique attenuates lymphatic sequelae but additional studies are required to establish the oncologic safety.

- To alleviate bladder dysfunction the optimal time for postoperative bladder catheterization needs to be explored and possible urotherapy interventions evaluated. A better understanding of the underlying causes, perhaps unrelated to nerve damage, is warranted.

10 SUMMARY IN SWEDISH (SAMMANFATTNING PÅ SVENSKA)

Livmoderhalscancer är globalt den fjärde vanligaste cancerformen hos kvinnor. Hälften av alla som drabbas är yngre än 50 år. Sjukdomen upptäcks och behandlas i regel tidigt och mer än 90% kan bli botade. Livmoderhalscancer i tidigt stadium behandlas genom att operera bort livmodern (radikal hysterektomi) samt regionala lymfkörtlar i bäckenet, och ibland även äggstockarna. Komplikationer från tarm och urinblåsa är vanliga, liksom bensvullnad och sexuella problem.

2005 introducerades robotassisterad laparoskopisk radikal hysterektomi (RRH) för kirurgisk behandling av livmoderhalscancer. RRH ansågs ha fördelar som t.ex kortare vårdtid och färre komplikationer jämfört med öppen radikal hysterektomi (ORH). Målet med projektet var att undersöka om RRH gav samma onkologiska säkerhet och var lika kostnadseffektivt som ORH. Dessutom följde vi kvinnornas funktionella besvär upp till ett år efter RRH.

Studie I inkluderade 304 kvinnor med livmoderhalscancer i tidigt stadium som genomgått RRH (n=149) och ORH (n=155) mellan 2006-2015 vid Karolinska Universitetssjukhuset. Kirurgiska komplikationer, kostnader och recidiv jämfördes. Postoperativa komplikationer (37%) och kostnader skilde sig inte åt mellan de kirurgiska teknikerna, men kvinnor som opererats med RRH hade i medeltal fyra dygn kortare vårdtid. Efter korrigering av kända riskfaktorer för recidiv som tumörstorlek, histologisk tumörtyp och lymfkörtelstatus sågs en ökar risk för recidiv efter RRH (HR 2.13; 95% CI, 1.06-4.26) i jämförelse med ORH.

I en nationell populationsbaserad studie mellan 2011-2017, innefattande 864 kvinnor med tidigt stadium av livmoderhalscancer **(Studie II),** jämfördes överlevnad mellan RRH (n=628) och ORH (n=236). Vi fann inte några skillnader i recidivfrekvens eller 5- års överlevnad mellan de kirurgiska teknikerna, även med hänsyn taget till de viktigaste prognostiska variablerna. Total 5-års överlevnad var 92% respektive 94% för ORH och RRH.

I Studie III: besvarade 26 kvinnor som genomgick RRH under 2011-2013 ett validerat frågeformulär före, samt ett år efter operation om livskvalitet, sexuell funktion och symtom från tarm, urinblåsa och eventuella lymfödem. Därtill mättes könshormoner. Resultaten visade att RRH i liten utsträckning påverkar tarm och sexuell funktion men att störningar i blåsfunktion (35%), och lymfdränage i benen (46%) var vanligt ett år efter kirurgi. Även depression och oro var signifikant ökade ett år efter operationen. Könshormonerna minskade signifikant, även hos premenopausala kvinnor som fick sina äggstockar bortopererade.

I **studie IV** svarade 27 kvinnor före, samt vid upprepade tillfällen upp till ett år efter operation på frågor om symtom från urinblåsan, och hur det påverkade livskvaliteten. Urinblåsefunktionen undersöktes med objektiva metoder (urodynamik) och via kvantifiering av nervtrådar som delades vid operationen. Studien visade att besvären från urinblåsan beror på en minskad kontraktionskraft och att en del kvinnor utvecklade urinläckage som kan bero krystning vid miktion. Symtomen minskade dock över tid, men kvarstod hos en del. I vissa fall uppgav även kvinnorna en sämre livskvalitet.

Data från våra registerbaserade studier är motstridiga, där den regionala studien visade en ökad risk för återfall efter robotkirurgi medan den nationella studien inte visade någon skillnad mellan metoderna. De olika resultaten kan bero på en inlärningskurva som ger sämre onkologiskt utfall när en ny operationsmetod introduceras. RRH medförde kortare vårdtid och färre intraoperativa komplikationer än ORH. Ingen skillnad noterades avseende postoperativa komplikationer och sjukvårdskostnader. RRH förefaller ha en liten effekt på sexuell funktion men många kvinnor har problem med blåstömning och lymfödem ett år efter kirurgi. Vi kunde inte visa att enbart nervskada i samband med kirurgin var orsak till blåstömningsbesvären utan även andra faktorer kan ha betydelse.

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12 REFERENCES

1. Ramirez PT, Frumovitz M, Pareja R, Lopez A, Vieira M, Ribeiro R, et al. Minimally Invasive versus Abdominal Radical Hysterectomy for Cervical Cancer. N Engl J Med. 2018;379(20):1895-904.

2. Melamed A, Margul DJ, Chen L, Keating NL, Del Carmen MG, Yang J, et al. Survival after Minimally Invasive Radical Hysterectomy for Early-Stage Cervical Cancer. N Engl J Med. 2018;379(20):1905-14.

3. Network NCC. NCCN clinical practice guidelines in oncology: cervical cancer version 1. [Available from: https://www.nccn.org/professionals/physician_gls/pdf/cervical_blocks.pdf.

4. Oncology ESoG. Laparoscopic radical hysterectomy: An ESGO statement: European Society of Gynaecological Oncology; 2019 [Available from: https://www.esgo.org/explore/council/laparoscopic-radical-hysterectomy-an-esgo-statement/.

5. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424.

6. Arbyn M, Weiderpass E, Bruni L, de Sanjose S, Saraiya M, Ferlay J, et al. Estimates of incidence and mortality of cervical cancer in 2018: a worldwide analysis. Lancet Glob Health. 2020;8(2):e191-e203.

7. Andrae B, Kemetli L, Sparen P, Silfverdal L, Strander B, Ryd W, et al. Screening-preventable cervical cancer risks: evidence from a nationwide audit in Sweden. J Natl Cancer Inst. 2008;100(9):622-9.

8. Ferlay J, Colombet M, Soerjomataram I, Mathers C, Parkin DM, Pineros M, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int J Cancer. 2019;144(8):1941-53.

9. Holland CM, Shafi MI. Radical hysterectomy. Best Pract Res Clin Obstet Gynaecol. 2005;19(3):387-401.

10. Bjurberg M, Holmberg E, Borgfeldt C, Floter-Radestad A, Dahm-Kahler P, Hjerpe E, et al. Primary treatment patterns and survival of cervical cancer in Sweden: A population-based Swedish Gynecologic Cancer Group Study. Gynecol Oncol. 2019;155(2):229-36.

11. zur Hausen H. Papillomavirus infections--a major cause of human cancers. Biochim Biophys Acta. 1996;1288(2):F55-78.

12. Bosch FX, Manos MM, Munoz N, Sherman M, Jansen AM, Peto J, et al. Prevalence of human papillomavirus in cervical cancer: a worldwide perspective. International biological study on cervical cancer (IBSCC) Study Group. J Natl Cancer Inst. 1995;87(11):796-802.

13. Ostor AG. Natural history of cervical intraepithelial neoplasia: a critical review. Int J Gynecol Pathol. 1993;12(2):186-92.

14. McCredie MR, Sharples KJ, Paul C, Baranyai J, Medley G, Jones RW, et al. Natural history of cervical neoplasia and risk of invasive cancer in women with cervical intraepithelial neoplasia 3: a retrospective cohort study. Lancet Oncol. 2008;9(5):425-34.

15. International Collaboration of Epidemiological Studies of Cervical C. Comparison of risk factors for invasive squamous cell carcinoma and adenocarcinoma of the cervix: collaborative reanalysis of individual data on 8,097 women with squamous cell carcinoma and 1,374 women with adenocarcinoma from 12 epidemiological studies. Int J Cancer. 2007;120(4):885-91.

16. Castellsague X, Bosch FX, Munoz N. Environmental co-factors in HPV carcinogenesis. Virus Res. 2002;89(2):191-9.

17. International Collaboration of Epidemiological Studies of Cervical C, Appleby P, Beral V, Berrington de Gonzalez A, Colin D, Franceschi S, et al. Cervical cancer and hormonal contraceptives: collaborative reanalysis of individual data for 16,573 women with cervical cancer and 35,509 women without cervical cancer from 24 epidemiological studies. Lancet. 2007;370(9599):1609-21.

18. Group FIS. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. N Engl J Med. 2007;356(19):1915-27.

19. cancercentrum R. Nationellt vårdprogram Livmoderhals och vaginalcancer. 2017.

20. Group FIS. Prophylactic efficacy of a quadrivalent human papillomavirus (HPV) vaccine in women with virological evidence of HPV infection. J Infect Dis. 2007;196(10):1438-46.

21. Joura EA, Giuliano AR, Iversen OE, Bouchard C, Mao C, Mehlsen J, et al. A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. N Engl J Med. 2015;372(8):711-23.

22. Harper DM, Franco EL, Wheeler C, Ferris DG, Jenkins D, Schuind A, et al. Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomised controlled trial. Lancet. 2004;364(9447):1757-65.

23. Organization WH. WHO Director-General hosts a Group of Experts for the elimination of cervical cancer as a public health problem 2019 [Available from: https://www.who.int/news-room/detail/26-08-2019-who-director-general-hosts-an-expert-meeting-to-check-and-challenge-the-emerging-global-strategy-to-eliminate-cervical-cancer.

24. Hall MT, Simms KT, Lew JB, Smith MA, Brotherton JM, Saville M, et al. The projected timeframe until cervical cancer elimination in Australia: a modelling study. Lancet Public Health. 2019;4(1):e19-e27.

25. cancercentrum R. Nationellt vårdprogram cervixcancerprevention 2019 [Available from: https://kunskapsbanken.cancercentrum.se/diagnoser/livmoderhalscancerprevention/.

26. Andrae B, Andersson TM, Lambert PC, Kemetli L, Silfverdal L, Strander B, et al. Screening and cervical cancer cure: population based cohort study. BMJ. 2012;344:e900.

27. Stern PL, van der Burg SH, Hampson IN, Broker TR, Fiander A, Lacey CJ, et al. Therapy of human papillomavirus-related disease. Vaccine. 2012;30 Suppl 5:F71-82.

28. Socialstyrelsen. Statistikdatabas för cancer 2019 [Available from: https://sdb.socialstyrelsen.se/if_can/resultat.aspx.

29. Dillner J, Sparen P, Andrae B, Strander B. [Cervical cancer has increased in Sweden in women who had a normal cell sample]. Lakartidningen. 2018;115.

30. Quinn MA, Benedet JL, Odicino F, Maisonneuve P, Beller U, Creasman WT, et al. Carcinoma of the cervix uteri. FIGO 26th Annual Report on the Results of Treatment in Gynecological Cancer. Int J Gynaecol Obstet. 2006;95 Suppl 1:S43-103.

31. Polterauer S, Grimm C, Hofstetter G, Concin N, Natter C, Sturdza A, et al. Nomogram prediction for overall survival of patients diagnosed with cervical cancer. Br J Cancer. 2012;107(6):918-24.

32. Horn LC, Bilek K, Fischer U, Einenkel J, Hentschel B. A cut-off value of 2 cm in tumor size is of prognostic value in surgically treated FIGO stage IB cervical cancer. Gynecol Oncol. 2014;134(1):42-6.

33. Horn LC, Fischer U, Raptis G, Bilek K, Hentschel B. Tumor size is of prognostic value in surgically treated FIGO stage II cervical cancer. Gynecol Oncol. 2007;107(2):310-5.

34. Sakuragi N. Up-to-date management of lymph node metastasis and the role of tailored lymphadenectomy in cervical cancer. Int J Clin Oncol. 2007;12(3):165-75.

35. Bergstrom R, Sparen P, Adami HO. Trends in cancer of the cervix uteri in Sweden following cytological screening. Br J Cancer. 1999;81(1):159-66.

36. Lacey JV, Jr., Brinton LA, Abbas FM, Barnes WA, Gravitt PE, Greenberg MD, et al. Oral contraceptives as risk factors for cervical adenocarcinomas and squamous cell carcinomas. Cancer Epidemiol Biomarkers Prev. 1999;8(12):1079-85.

37. Wright JD, Grigsby PW, Brooks R, Powell MA, Gibb RK, Gao F, et al. Utility of parametrectomy for early stage cervical cancer treated with radical hysterectomy. Cancer. 2007;110(6):1281-6.

38. Covens A, Rosen B, Murphy J, Laframboise S, DePetrillo AD, Lickrish G, et al. How important is removal of the parametrium at surgery for carcinoma of the cervix? Gynecol Oncol. 2002;84(1):145-9.

39. Singh P, Tripcony L, Nicklin J. Analysis of prognostic variables, development of predictive models, and stratification of risk groups in surgically treated FIGO early-stage (IA-IIA) carcinoma cervix. Int J Gynecol Cancer. 2012;22(1):115-22.

40. Pecorelli S. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. Int J Gynaecol Obstet. 2009;105(2):103-4.

41. Bhatla N, Berek JS, Cuello Fredes M, Denny LA, Grenman S, Karunaratne K, et al. Revised FIGO staging for carcinoma of the cervix uteri. Int J Gynaecol Obstet. 2019;145(1):129-35.

42. Pecorelli S, Zigliani L, Odicino F. Revised FIGO staging for carcinoma of the cervix. Int J Gynaecol Obstet. 2009;105(2):107-8.

43. Qin Y, Peng Z, Lou J, Liu H, Deng F, Zheng Y. Discrepancies between clinical staging and pathological findings of operable cervical carcinoma with stage IB-IIB: a retrospective analysis of 818 patients. Aust N Z J Obstet Gynaecol. 2009;49(5):542-4.

44. Zhang W, Chen C, Liu P, Li W, Hao M, Zhao W, et al. Impact of pelvic MRI in routine clinical practice on staging of IB1-IIA2 cervical cancer. Cancer Manag Res. 2019;11:3603-9.

45. Amin MB, Greene FL, Edge SB, Compton CC, Gershenwald JE, Brookland RK, et al. The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge

from a population-based to a more "personalized" approach to cancer staging. CA Cancer J Clin. 2017;67(2):93-9.

46. Landoni F, Maneo A, Colombo A, Placa F, Milani R, Perego P, et al. Randomised study of radical surgery versus radiotherapy for stage Ib-IIa cervical cancer. Lancet. 1997;350(9077):535-40.

47. Kupets R, Thomas GM, Covens A. Is there a role for pelvic lymph node debulking in advanced cervical cancer? Gynecol Oncol. 2002;87(2):163-70.

48. Green J, Kirwan J, Tierney J, Vale C, Symonds P, Fresco L, et al. Concomitant chemotherapy and radiation therapy for cancer of the uterine cervix. Cochrane Database Syst Rev. 2005(3):CD002225.

49. Rob L, Skapa P, Robova H. Fertility-sparing surgery in patients with cervical cancer. Lancet Oncol. 2011;12(2):192-200.

50. van Kol KGG, Vergeldt TFM, Bekkers RLM. Abdominal radical trachelectomy versus chemotherapy followed by vaginal radical trachelectomy in stage 1B2 (FIGO 2018) cervical cancer. A systematic review on fertility and recurrence rates. Gynecol Oncol. 2019;155(3):515-21.

51. Shimada M, Kigawa J, Nishimura R, Yamaguchi S, Kuzuya K, Nakanishi T, et al. Ovarian metastasis in carcinoma of the uterine cervix. Gynecol Oncol. 2006;101(2):234-7.

52. Sedlis A, Bundy BN, Rotman MZ, Lentz SS, Muderspach LI, Zaino RJ. A randomized trial of pelvic radiation therapy versus no further therapy in selected patients with stage IB carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy: A Gynecologic Oncology Group Study. Gynecol Oncol. 1999;73(2):177-83.

53. McCann GA, Taege SK, Boutsicaris CE, Phillips GS, Eisenhauer EL, Fowler JM, et al. The impact of close surgical margins after radical hysterectomy for early-stage cervical cancer. Gynecol Oncol. 2013;128(1):44-8.

54. Estape RE, Angioli R, Madrigal M, Janicek M, Gomez C, Penalver M, et al. Close vaginal margins as a prognostic factor after radical hysterectomy. Gynecol Oncol. 1998;68(3):229-32.

55. Peters WA, 3rd, Liu PY, Barrett RJ, 2nd, Stock RJ, Monk BJ, Berek JS, et al. Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. J Clin Oncol. 2000;18(8):1606-13.

56. Kinney WK, Alvarez RD, Reid GC, Schray MF, Soong SJ, Morley GW, et al. Value of adjuvant whole-pelvis irradiation after Wertheim hysterectomy for early-stage squamous carcinoma of the cervix with pelvic nodal metastasis: a matched-control study. Gynecol Oncol. 1989;34(3):258-62.

57. Charra-Brunaud C, Harter V, Delannes M, Haie-Meder C, Quetin P, Kerr C, et al. Impact of 3D image-based PDR brachytherapy on outcome of patients treated for cervix carcinoma in France: results of the French STIC prospective study. Radiother Oncol. 2012;103(3):305-13.

58. Ribeiro I, Janssen H, De Brabandere M, Nulens A, De Bal D, Vergote I, et al. Long term experience with 3D image guided brachytherapy and clinical outcome in cervical cancer patients. Radiother Oncol. 2016;120(3):447-54.

59. Swamidas J, Kirisits C, De Brabandere M, Hellebust TP, Siebert FA, Tanderup K. Image registration, contour propagation and dose accumulation of external beam and brachytherapy in gynecological radiotherapy. Radiother Oncol. 2020;143:1-11.

60. Chapman CH, Polan D, Vineberg K, Jolly S, Maturen KE, Brock KK, et al. Deformable image registration-based contour propagation yields clinically acceptable plans for MRI-based cervical cancer brachytherapy planning. Brachytherapy. 2018;17(2):360-7.

61. Verleye L, Vergote I, Reed N, Ottevanger PB. Quality assurance for radical hysterectomy for cervical cancer: the view of the European Organization for Research and Treatment of Cancer--Gynecological Cancer Group (EORTC-GCG). Ann Oncol. 2009;20(10):1631-8.

62. Hertel H, Kohler C, Michels W, Possover M, Tozzi R, Schneider A. Laparoscopic-assisted radical vaginal hysterectomy (LARVH): prospective evaluation of 200 patients with cervical cancer. Gynecol Oncol. 2003;90(3):505-11.

63. Querleu D. Laparoscopic radical hysterectomy. Am J Obstet Gynecol. 1993;168(5):1643-5.

64. Boggess JF. Robotic surgery in gynecologic oncology: evolution of a new surgical paradigm. J Robot Surg. 2007;1(1):31-7.

65. Boggess JF, Gehrig PA, Cantrell L, Shafer A, Ridgway M, Skinner EN, et al. A case-control study of robot-assisted type III radical hysterectomy with pelvic lymph node dissection compared with open radical hysterectomy. Am J Obstet Gynecol. 2008;199(4):357 e1-7.

66. Dursun P, Gultekin M, Ayhan A. The history of radical hysterectomy. J Low Genit Tract Dis. 2011;15(3):235-45.

67. Maas CP, Trimbos JB, DeRuiter MC, van de Velde CJ, Kenter GG. Nerve sparing radical hysterectomy: latest developments and historical perspective. Crit Rev Oncol Hematol. 2003;48(3):271-9.

68. Meigs JV. Radical hysterectomy with bilateral pelvic lymph node dissections; a report of 100 patients operated on five or more years ago. Am J Obstet Gynecol. 1951;62(4):854-70.

69. Pieterse QD, Kenter GG, Gaarenstroom KN, Peters AA, Willems SM, Fleuren GJ, et al. The number of pelvic lymph nodes in the quality control and prognosis of radical hysterectomy for the treatment of cervical cancer. Eur J Surg Oncol. 2007;33(2):216-21.

70. Hockel M, Wolf B, Schmidt K, Mende M, Aktas B, Kimmig R, et al. Surgical resection based on ontogenetic cancer field theory for cervical cancer: mature results from a single-centre, prospective, observational, cohort study. Lancet Oncol. 2019;20(9):1316-26.

71. Wolf B, Ganzer R, Stolzenburg JU, Hentschel B, Horn LC, Hockel M. Extended mesometrial resection (EMMR): Surgical approach to the treatment of locally advanced cervical cancer based on the theory of ontogenetic cancer fields. Gynecol Oncol. 2017;146(2):292-8.

72. Hockel M, Horn LC, Hentschel B, Hockel S, Naumann G. Total mesometrial resection: high resolution nerve-sparing radical hysterectomy based on developmentally defined surgical anatomy. Int J Gynecol Cancer. 2003;13(6):791-803.

73. Landoni F, Maneo A, Cormio G, Perego P, Milani R, Caruso O, et al. Class II versus class III radical hysterectomy in stage IB-IIA cervical cancer: a prospective randomized study. Gynecol Oncol. 2001;80(1):3-12.

74. Landoni F, Maneo A, Zapardiel I, Zanagnolo V, Mangioni C. Class I versus class III radical hysterectomy in stage IB1-IIA cervical cancer. A prospective randomized study. Eur J Surg Oncol. 2012;38(3):203-9.

75. Naik R, Cross P, Nayar A, Mayadevi S, Lopes A, Godfrey K, et al. Conservative surgical management of small-volume stage IB1 cervical cancer. BJOG. 2007;114(8):958-63.

76. Sia TY, Chen L, Melamed A, Tergas AI, Khoury-Collado F, Hou JY, et al. Trends in Use and Effect on Survival of Simple Hysterectomy for Early-Stage Cervical Cancer. Obstet Gynecol. 2019;134(6):1132-43.

77. Biliatis I, Kucukmetin A, Patel A, Ratnavelu N, Cross P, Chattopadhyay S, et al. Small volume stage 1B1 cervical cancer: Is radical surgery still necessary? Gynecol Oncol. 2012;126(1):73-7.

78. Chen L, Zhang WN, Zhang SM, Gao Y, Zhang TH, Zhang P. Class I hysterectomy in stage Ia2-Ib1 cervical cancer. Wideochir Inne Tech Maloinwazyjne. 2018;13(4):494-500.

79. Medicine USNLo. Radical Versus Simple Hysterectomy and Pelvic Node Dissection With Low-risk Early Stage Cervical Cancer (SHAPE) 2012 [Available from: https://clinicaltrials.gov/ct2/show/NCT01658930?term=SHAPE&cond=Cervical+Cancer&draw=2&rank=1.

80. Plante M, van Trommel N, Lheureux S, Oza AM, Wang L, Sikorska K, et al. FIGO 2018 stage IB2 (2-4 cm) Cervical cancer treated with Neo-adjuvant chemotherapy followed by fertility Sparing Surgery (CONTESSA); Neo-Adjuvant Chemotherapy and Conservative Surgery in Cervical Cancer to Preserve Fertility (NEOCON-F). A PMHC, DGOG, GCIG/CCRN and multicenter study. Int J Gynecol Cancer. 2019;29(5):969-75.

81. Piver MS, Rutledge F, Smith JP. Five classes of extended hysterectomy for women with cervical cancer. Obstet Gynecol. 1974;44(2):265-72.

82. Querleu D, Morrow CP. Classification of radical hysterectomy. Lancet Oncol. 2008;9(3):297-303.

83. Cibula D, Planchamp F, Fischerova D, Fotopoulou C, Kohler C, Landoni F, et al. European Society of Gynaecological Oncology quality indicators for surgical treatment of cervical cancer. Int J Gynecol Cancer. 2020;30(1):3-14.

84. Sakuragi N, Murakami G, Konno Y, Kaneuchi M, Watari H. Nerve-sparing radical hysterectomy in the precision surgery for cervical cancer. J Gynecol Oncol. 2020;31(3):e49.

85. Maas CP, Kenter GG, Trimbos JB, Deruiter MC. Anatomical basis for nerve-sparing radical hysterectomy: immunohistochemical study of the pelvic autonomic nerves. Acta Obstet Gynecol Scand. 2005;84(9):868-74.

86. Ercoli A, Delmas V, Gadonneix P, Fanfani F, Villet R, Paparella P, et al. Classical and nerve-sparing radical hysterectomy: an evaluation of the risk of injury to the autonomous pelvic nerves. Surg Radiol Anat. 2003;25(3-4):200-6.

87. Laterza RM, Salvatore S, Ghezzi F, Serati M, Umek W, Koelbl H. Urinary and anal dysfunction after laparoscopic versus laparotomic radical hysterectomy. Eur J Obstet Gynecol Reprod Biol. 2015;194:11-6.

88. Pieterse QD, Kenter GG, Maas CP, de Kroon CD, Creutzberg CL, Trimbos JB, et al. Self-reported sexual, bowel and bladder function in cervical cancer patients following different treatment modalities: longitudinal prospective cohort study. Int J Gynecol Cancer. 2013;23(9):1717-25.

89. Chen L, Zhang WN, Zhang SM, Yang ZH, Zhang P. Effect of laparoscopic nerve-sparing radical hysterectomy on bladder function, intestinal function recovery and quality of sexual life in patients with cervical carcinoma. Asian Pac J Cancer Prev. 2014;15(24):10971-5.

90. Lee SH, Bae JW, Han M, Cho YJ, Park JW, Oh SR, et al. Efficacy of nerve-sparing radical hysterectomy vs. conventional radical hysterectomy in early-stage cervical cancer: A systematic review and meta-analysis. Mol Clin Oncol. 2020;12(2):160-8.

91. Loizzi V, Cormio G, Lobascio PL, Marino F, De Fazio M, Falagario M, et al. Bowel dysfunction following nerve-sparing radical hysterectomy for cervical cancer: a prospective study. Oncology. 2014;86(4):239-43.

92. Wang YZ, Deng L, Xu HC, Zhang Y, Liang ZQ. Laparoscopy versus laparotomy for the management of early stage cervical cancer. BMC Cancer. 2015;15:928.

93. Cibula D, Abu-Rustum NR, Benedetti-Panici P, Kohler C, Raspagliesi F, Querleu D, et al. New classification system of radical hysterectomy: emphasis on a three-dimensional anatomic template for parametrial resection. Gynecol Oncol. 2011;122(2):264-8.

94. Fujii S, Takakura K, Matsumura N, Higuchi T, Yura S, Mandai M, et al. Anatomic identification and functional outcomes of the nerve sparing Okabayashi radical hysterectomy. Gynecol Oncol. 2007;107(1):4-13.

95. Kelley WE, Jr. The evolution of laparoscopy and the revolution in surgery in the decade of the 1990s. JSLS. 2008;12(4):351-7.

96. Litynski GS. Endoscopic surgery: the history, the pioneers. World J Surg. 1999;23(8):745-53.

97. Walker JL, Piedmonte MR, Spirtos NM, Eisenkop SM, Schlaerth JB, Mannel RS, et al. Recurrence and survival after random assignment to laparoscopy versus laparotomy for comprehensive surgical staging of uterine cancer: Gynecologic Oncology Group LAP2 Study. J Clin Oncol. 2012;30(7):695-700.

98. Janda M, Gebski V, Davies LC, Forder P, Brand A, Hogg R, et al. Effect of Total Laparoscopic Hysterectomy vs Total Abdominal Hysterectomy on Disease-Free Survival Among Women With Stage I Endometrial Cancer: A Randomized Clinical Trial. JAMA. 2017;317(12):1224-33.

99. Nezhat F, Nezhat C, Gordon S, Wilkins E. Laparoscopic versus abdominal hysterectomy. J Reprod Med. 1992;37(3):247-50.

100. Nezhat CR, Burrell MO, Nezhat FR, Benigno BB, Welander CE. Laparoscopic radical hysterectomy with paraaortic and pelvic node dissection. Am J Obstet Gynecol. 1992;166(3):864-5.

101. Magrina JF, Kho RM, Weaver AL, Montero RP, Magtibay PM. Robotic radical hysterectomy: comparison with laparoscopy and laparotomy. Gynecol Oncol. 2008;109(1):86-91.

102. Hoogendam JP, Verheijen RH, Wegner I, Zweemer RP. Oncological outcome and long-term complications in robot-assisted radical surgery for early stage cervical cancer: an observational cohort study. BJOG. 2014;121(12):1538-45.

103. Geetha P, Nair MK. Laparoscopic, robotic and open method of radical hysterectomy for cervical cancer: A systematic review. J Minim Access Surg. 2012;8(3):67-73.

104. Nam JH, Park JY, Kim DY, Kim JH, Kim YM, Kim YT. Laparoscopic versus open radical hysterectomy in early-stage cervical cancer: long-term survival outcomes in a matched cohort study. Ann Oncol. 2012;23(4):903-11.

105. Bogani G, Cromi A, Uccella S, Serati M, Casarin J, Pinelli C, et al. Laparoscopic versus open abdominal management of cervical cancer: long-term results from a propensity-matched analysis. J Minim Invasive Gynecol. 2014;21(5):857-62.

106. Ditto A, Martinelli F, Bogani G, Gasparri ML, Di Donato V, Zanaboni F, et al. Implementation of laparoscopic approach for type B radical hysterectomy: a comparison with open surgical operations. Eur J Surg Oncol. 2015;41(1):34-9.

107. Sert BM, Boggess JF, Ahmad S, Jackson AL, Stavitzski NM, Dahl AA, et al. Robot-assisted versus open radical hysterectomy: A multi-institutional experience for early-stage cervical cancer. Eur J Surg Oncol. 2016;42(4):513-22.

108. Abu-Rustum NR, Gemignani ML, Moore K, Sonoda Y, Venkatraman E, Brown C, et al. Total laparoscopic radical hysterectomy with pelvic lymphadenectomy using the argon-beam coagulator: pilot data and comparison to laparotomy. Gynecol Oncol. 2003;91(2):402-9.

109. Hwang JH, Yoo HJ, Joo J, Kim S, Lim MC, Song YJ, et al. Learning curve analysis of laparoscopic radical hysterectomy and lymph node dissection in early cervical cancer. Eur J Obstet Gynecol Reprod Biol. 2012;163(2):219-23.

110. Shazly SA, Murad MH, Dowdy SC, Gostout BS, Famuyide AO. Robotic radical hysterectomy in early stage cervical cancer: A systematic review and meta-analysis. Gynecol Oncol. 2015;138(2):457-71.

111. Nie JC, Yan AQ, Liu XS. Robotic-Assisted Radical Hysterectomy Results in Better Surgical Outcomes Compared With the Traditional Laparoscopic Radical Hysterectomy for the Treatment of Cervical Cancer. Int J Gynecol Cancer. 2017;27(9):1990-9.

112. Luo C, Liu M, Li X. Efficacy and safety outcomes of robotic radical hysterectomy in Chinese older women with cervical cancer compared with laparoscopic radical hysterectomy. BMC Womens Health. 2018;18(1):61.

113. Tinelli R, Malzoni M, Cosentino F, Perone C, Fusco A, Cicinelli E, et al. Robotics versus laparoscopic radical hysterectomy with lymphadenectomy in patients with early cervical cancer: a multicenter study. Ann Surg Oncol. 2011;18(9):2622-8.

114. Sert BM, Abeler VM. Robotic-assisted laparoscopic radical hysterectomy (Piver type III) with pelvic node dissection--case report. Eur J Gynaecol Oncol. 2006;27(5):531-3.

115. Gil-Moreno A, Carbonell-Socias M, Salicru S, Centeno-Mediavilla C, Franco-Camps S, Colas E, et al. Radical Hysterectomy: Efficacy and Safety in the Dawn of Minimally Invasive Techniques. J Minim Invasive Gynecol. 2019;26(3):492-500.

116. Mendivil AA, Rettenmaier MA, Abaid LN, Brown JV, 3rd, Micha JP, Lopez KL, et al. Survival rate comparisons amongst cervical cancer patients treated with an open, robotic-assisted or laparoscopic radical hysterectomy: A five year experience. Surg Oncol. 2016;25(1):66-71.

117. Wallin E, Floter Radestad A, Falconer H. Introduction of robot-assisted radical hysterectomy for early stage cervical cancer: impact on complications, costs and oncologic outcome. Acta Obstet Gynecol Scand. 2017.

118. Zanagnolo V, Minig L, Rollo D, Tomaselli T, Aletti G, Bocciolone L, et al. Clinical and Oncologic Outcomes of Robotic Versus Abdominal Radical Hysterectomy for Women With Cervical Cancer: Experience at a Referral Cancer Center. Int J Gynecol Cancer. 2016;26(3):568-74.

119. Sert B, Abeler V. Robotic radical hysterectomy in early-stage cervical carcinoma patients, comparing results with total laparoscopic radical hysterectomy cases. The future is now? Int J Med Robot. 2007;3(3):224-8.

120. O'Neill M, Moran PS, Teljeur C, O'Sullivan OE, O'Reilly BA, Hewitt M, et al. Robot-assisted hysterectomy compared to open and laparoscopic approaches: systematic review and meta-analysis. Arch Gynecol Obstet. 2013;287(5):907-18.

121. Shah CA, Beck T, Liao JB, Giannakopoulos NV, Veljovich D, Paley P. Surgical and oncologic outcomes after robotic radical hysterectomy as compared to open radical hysterectomy in the treatment of early cervical cancer. J Gynecol Oncol. 2017;28(6):e82.

122. Soliman PT, Frumovitz M, Sun CC, Dos Reis R, Schmeler KM, Nick AM, et al. Radical hysterectomy: a comparison of surgical approaches after adoption of robotic surgery in gynecologic oncology. Gynecol Oncol. 2011;123(2):333-6.

123. Cantrell LA, Mendivil A, Gehrig PA, Boggess JF. Survival outcomes for women undergoing type III robotic radical hysterectomy for cervical cancer: a 3-year experience. Gynecol Oncol. 2010;117(2):260-5.

124. Segaert A, Traen K, Van Trappen P, Peeters F, Leunen K, Goffin F, et al. Robot-Assisted Radical Hysterectomy in Cervical Carcinoma: The Belgian Experience. Int J Gynecol Cancer. 2015;25(9):1690-6.

125. Sert MB, Abeler V. Robot-assisted laparoscopic radical hysterectomy: comparison with total laparoscopic hysterectomy and abdominal radical hysterectomy; one surgeon's experience at the Norwegian Radium Hospital. Gynecol Oncol. 2011;121(3):600-4.

126. Koh W-J, Greer BE, Abu-Rustum NR, Apte SM, Campos SM, Cho KR, et al. Cervical cancer, version 2.2015. 2015;13(4):395-404.

127. Cibula D, Potter R, Planchamp F, Avall-Lundqvist E, Fischerova D, Haie Meder C, et al. The European Society of Gynaecological Oncology/European Society for Radiotherapy and Oncology/European Society of Pathology guidelines for the management of patients with cervical cancer. Radiother Oncol. 2018;127(3):404-16.

128. Obermair A, Gebski V, Frumovitz M, Soliman PT, Schmeler KM, Levenback C, et al. A phase III randomized clinical trial comparing laparoscopic or robotic radical

hysterectomy with abdominal radical hysterectomy in patients with early stage cervical cancer. J Minim Invasive Gynecol. 2008;15(5):584-8.

129. Wang Y, Li B, Ren F, Song Z, Ouyang L, Liu K. Survival After Minimally Invasive vs. Open Radical Hysterectomy for Cervical Cancer: A Meta-Analysis. Front Oncol. 2020;10:1236.

130. Doo DW, Kirkland CT, Griswold LH, McGwin G, Huh WK, Leath CA, 3rd, et al. Comparative outcomes between robotic and abdominal radical hysterectomy for IB1 cervical cancer: Results from a single high volume institution. Gynecol Oncol. 2019;153(2):242-7.

131. Chen B, Ji M, Li P, Liu P, Zou W, Zhao Z, et al. Comparison between robot-assisted radical hysterectomy and abdominal radical hysterectomy for cervical cancer: A multicentre retrospective study. Gynecol Oncol. 2020;157(2):429-36.

132. Uppal S, Gehrig PA, Peng K, Bixel KL, Matsuo K, Vetter MH, et al. Recurrence Rates in Patients With Cervical Cancer Treated With Abdominal Versus Minimally Invasive Radical Hysterectomy: A Multi-Institutional Retrospective Review Study. J Clin Oncol. 2020;38(10):1030-40.

133. Cusimano MC, Baxter NN, Gien LT, Moineddin R, Liu N, Dossa F, et al. Impact of surgical approach on oncologic outcomes in women undergoing radical hysterectomy for cervical cancer. Am J Obstet Gynecol. 2019;221(6):619 e1- e24.

134. Nitecki R, Ramirez PT, Frumovitz M, Krause KJ, Tergas AI, Wright JD, et al. Survival After Minimally Invasive vs Open Radical Hysterectomy for Early-Stage Cervical Cancer: A Systematic Review and Meta-analysis. JAMA Oncology. 2020;6(7):1019-27.

135. Obermair A, Asher R, Pareja R, Frumovitz M, Lopez A, Moretti-Marques R, et al. Incidence of adverse events in minimally invasive vs open radical hysterectomy in early cervical cancer: results of a randomized controlled trial. Am J Obstet Gynecol. 2020;222(3):249 e1- e10.

136. Alfonzo E, Wallin E, Ekdahl L, Staf C, Radestad AF, Reynisson P, et al. No survival difference between robotic and open radical hysterectomy for women with early-stage cervical cancer: results from a nationwide population-based cohort study. Eur J Cancer. 2019;116:169-77.

137. Bergmark K, Avall-Lundqvist E, Dickman PW, Henningsohn L, Steineck G. Lymphedema and bladder-emptying difficulties after radical hysterectomy for early cervical cancer and among population controls. Int J Gynecol Cancer. 2006;16(3):1130-9.

138. Beesley V, Janda M, Eakin E, Obermair A, Battistutta D. Lymphedema after gynecological cancer treatment : prevalence, correlates, and supportive care needs. Cancer. 2007;109(12):2607-14.

139. Hareyama H, Hada K, Goto K, Watanabe S, Hakoyama M, Oku K, et al. Prevalence, classification, and risk factors for postoperative lower extremity lymphedema in women with gynecologic malignancies: a retrospective study. Int J Gynecol Cancer. 2015;25(4):751-7.

140. Morgan PA, Franks PJ, Moffatt CJ. Health-related quality of life with lymphoedema: a review of the literature. Int Wound J. 2005;2(1):47-62.

141. Kim SI, Lim MC, Lee JS, Lee Y, Park K, Joo J, et al. Impact of lower limb lymphedema on quality of life in gynecologic cancer survivors after pelvic lymph node dissection. Eur J Obstet Gynecol Reprod Biol. 2015;192:31-6.

142. Mansel RE, Fallowfield L, Kissin M, Goyal A, Newcombe RG, Dixon JM, et al. Randomized multicenter trial of sentinel node biopsy versus standard axillary treatment in operable breast cancer: the ALMANAC Trial. J Natl Cancer Inst. 2006;98(9):599-609.

143. Tax C, Rovers MM, de Graaf C, Zusterzeel PL, Bekkers RL. The sentinel node procedure in early stage cervical cancer, taking the next step; a diagnostic review. Gynecol Oncol. 2015;139(3):559-67.

144. Wu Y, Li Z, Wu H, Yu J. Sentinel lymph node biopsy in cervical cancer: A meta-analysis. Mol Clin Oncol. 2013;1(6):1025-30.

145. Cibula D, Abu-Rustum NR, Dusek L, Slama J, Zikan M, Zaal A, et al. Bilateral ultrastaging of sentinel lymph node in cervical cancer: Lowering the false-negative rate and improving the detection of micrometastasis. Gynecol Oncol. 2012;127(3):462-6.

146. Geppert B, Lonnerfors C, Bollino M, Arechvo A, Persson J. A study on uterine lymphatic anatomy for standardization of pelvic sentinel lymph node detection in endometrial cancer. Gynecol Oncol. 2017;145(2):256-61.

147. Lecuru FR, McCormack M, Hillemanns P, Anota A, Leitao M, Mathevet P, et al. SENTICOL III: an international validation study of sentinel node biopsy in early cervical cancer. A GINECO, ENGOT, GCIG and multicenter study. Int J Gynecol Cancer. 2019;29(4):829-34.

148. samverkan Rci. Nationellt vårdprogram livmoderhals- och vaginalcancer 2020 [Available from: https://kunskapsbanken.cancercentrum.se/diagnoser/livmoderhals-och-vaginalcancer/vardprogram/.

149. Services SAfHTAaAoS. Hälsoekonomiska Utvärderingar 2017. [Available from: https://www.sbu.se/globalassets/ebm/metodbok/sbushandbok_kapitel11.pdf.

150. Forsmark A, Gehrman J, Angenete E, Bjartell A, Bjorholt I, Carlsson S, et al. Health Economic Analysis of Open and Robot-assisted Laparoscopic Surgery for Prostate Cancer Within the Prospective Multicentre LAPPRO Trial. Eur Urol. 2018;74(6):816-24.

151. Close A, Robertson C, Rushton S, Shirley M, Vale L, Ramsay C, et al. Comparative cost-effectiveness of robot-assisted and standard laparoscopic prostatectomy as alternatives to open radical prostatectomy for treatment of men with localised prostate cancer: a health technology assessment from the perspective of the UK National Health Service. Eur Urol. 2013;64(3):361-9.

152. Lonnerfors C, Reynisson P, Persson J. A randomized trial comparing vaginal and laparoscopic hysterectomy vs robot-assisted hysterectomy. J Minim Invasive Gynecol. 2015;22(1):78-86.

153. Salehi S, Avall-Lundqvist E, Legerstam B, Carlson JW, Falconer H. Robot-assisted laparoscopy versus laparotomy for infrarenal paraaortic lymphadenectomy in women with high-risk endometrial cancer: A randomised controlled trial. Eur J Cancer. 2017;79:81-9.

154. Zakhari A, Czuzoj-Shulman N, Spence AR, Gotlieb WH, Abenhaim HA. Laparoscopic and robot-assisted hysterectomy for uterine cancer: a comparison of costs and complications. Am J Obstet Gynecol. 2015;213(5):665 e1-7.

155. Reynisson P, Persson J. Hospital costs for robot-assisted laparoscopic radical hysterectomy and pelvic lymphadenectomy. Gynecol Oncol. 2013;130(1):95-9.

156. Kristensen SE, Mosgaard BJ, Rosendahl M, Dalsgaard T, Bjorn SF, Froding LP, et al. Robot-assisted surgery in gynecological oncology: current status and controversies on patient benefits, cost and surgeon conditions - a systematic review. Acta Obstet Gynecol Scand. 2017;96(3):274-85.

157. Moinpour CM. Measuring quality of life: an emerging science. Semin Oncol. 1994;21(5 Suppl 10):48-60; discussion -3.

158. Testa MA, Simonson DC. Assessment of quality-of-life outcomes. N Engl J Med. 1996;334(13):835-40.

159. Coates A, Gebski V, Signorini D, Murray P, McNeil D, Byrne M, et al. Prognostic value of quality-of-life scores during chemotherapy for advanced breast cancer. Australian New Zealand Breast Cancer Trials Group. J Clin Oncol. 1992;10(12):1833-8.

160. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85(5):365-76.

161. Hua CH, Guo HM, Guan XL, Kong FJ, Hou RJ, Zhang XY, et al. Validation of the European Organization for Research and Treatment of Cancer cervical cancer module for Chinese patients with cervical cancer. Patient Prefer Adherence. 2013;7:1061-6.

162. Osoba D, Zee B, Pater J, Warr D, Kaizer L, Latreille J. Psychometric properties and responsiveness of the EORTC quality of Life Questionnaire (QLQ-C30) in patients with breast, ovarian and lung cancer. Qual Life Res. 1994;3(5):353-64.

163. Greimel ER, Kuljanic Vlasic K, Waldenstrom AC, Duric VM, Jensen PT, Singer S, et al. The European Organization for Research and Treatment of Cancer (EORTC) Quality-of-Life questionnaire cervical cancer module: EORTC QLQ-CX24. Cancer. 2006;107(8):1812-22.

164. Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E, Bonomi A, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. J Clin Oncol. 1993;11(3):570-9.

165. Omerov P, Steineck G, Runeson B, Christensson A, Kreicbergs U, Pettersen R, et al. Preparatory studies to a population-based survey of suicide-bereaved parents in Sweden. Crisis. 2013;34(3):200-10.

166. Bergmark K, Avall-Lundqvist E, Dickman PW, Henningsohn L, Steineck G. Vaginal changes and sexuality in women with a history of cervical cancer. N Engl J Med. 1999;340(18):1383-9.

167. Vistad I, Fossa SD, Dahl AA. A critical review of patient-rated quality of life studies of long-term survivors of cervical cancer. Gynecol Oncol. 2006;102(3):563-72.

168. Ye S, Yang J, Cao D, Lang J, Shen K. A systematic review of quality of life and sexual function of patients with cervical cancer after treatment. Int J Gynecol Cancer. 2014;24(7):1146-57.

169. Le Borgne G, Mercier M, Woronoff AS, Guizard AV, Abeilard E, Caravati-Jouvenceaux A, et al. Quality of life in long-term cervical cancer survivors: a population-based study. Gynecol Oncol. 2013;129(1):222-8.

170. Mantegna G, Petrillo M, Fuoco G, Venditti L, Terzano S, Anchora LP, et al. Long-term prospective longitudinal evaluation of emotional distress and quality of life in

cervical cancer patients who remained disease-free 2-years from diagnosis. BMC Cancer. 2013;13:127.

171. Steen R, Dahl AA, Hess SL, Kiserud CE. A study of chronic fatigue in Norwegian cervical cancer survivors. Gynecol Oncol. 2017;146(3):630-5.

172. Carter J, Chi DS, Brown CL, Abu-Rustum NR, Sonoda Y, Aghajanian C, et al. Cancer-related infertility in survivorship. Int J Gynecol Cancer. 2010;20(1):2-8.

173. Kirchhoff AC, Yi J, Wright J, Warner EL, Smith KR. Marriage and divorce among young adult cancer survivors. J Cancer Surviv. 2012;6(4):441-50.

174. Sekse RJT, Dunberger G, Olesen ML, Osterbye M, Seibaek L. Lived experiences and quality of life after gynaecological cancer-An integrative review. J Clin Nurs. 2019;28(9-10):1393-421.

175. Toritani K, Watanabe J, Nakagawa K, Suwa Y, Suwa H, Ishibe A, et al. Randomized controlled trial to evaluate laparoscopic versus open surgery in transverse and descending colon cancer patients. Int J Colorectal Dis. 2019;34(7):1211-20.

176. Lacy AM, Garcia-Valdecasas JC, Delgado S, Castells A, Taura P, Pique JM, et al. Laparoscopy-assisted colectomy versus open colectomy for treatment of non-metastatic colon cancer: a randomised trial. Lancet. 2002;359(9325):2224-9.

177. Salehi S, Brandberg Y, Avall-Lundqvist E, Suzuki C, Johansson H, Legerstam B, et al. Long-term quality of life after comprehensive surgical staging of high-risk endometrial cancer - results from the RASHEC trial. Acta Oncol. 2018;57(12):1671-6.

178. Kornblith AB, Huang HQ, Walker JL, Spirtos NM, Rotmensch J, Cella D. Quality of life of patients with endometrial cancer undergoing laparoscopic international federation of gynecology and obstetrics staging compared with laparotomy: a Gynecologic Oncology Group study. J Clin Oncol. 2009;27(32):5337-42.

179. Frumovitz M, Obermair A, Coleman RL, Pareja R, Lopez A, Ribero R, et al. Quality of life in patients with cervical cancer after open versus minimally invasive radical hysterectomy (LACC): a secondary outcome of a multicentre, randomised, open-label, phase 3, non-inferiority trial. Lancet Oncol. 2020;21(6):851-60.

180. Bloom JR, Petersen DM, Kang SH. Multi-dimensional quality of life among long-term (5+ years) adult cancer survivors. Psychooncology. 2007;16(8):691-706.

181. Jensen PT, Groenvold M, Klee MC, Thranov I, Petersen MA, Machin D. Early-stage cervical carcinoma, radical hysterectomy, and sexual function. A longitudinal study. Cancer. 2004;100(1):97-106.

182. Froeding LP, Ottosen C, Rung-Hansen H, Svane D, Mosgaard BJ, Jensen PT. Sexual functioning and vaginal changes after radical vaginal trachelectomy in early stage cervical cancer patients: a longitudinal study. J Sex Med. 2014;11(2):595-604.

183. Xiao M, Gao H, Bai H, Zhang Z. Quality of life and sexuality in disease-free survivors of cervical cancer after radical hysterectomy alone: A comparison between total laparoscopy and laparotomy. Medicine (Baltimore). 2016;95(36):e4787.

184. Zhou W, Yang X, Dai Y, Wu Q, He G, Yin G. Survey of cervical cancer survivors regarding quality of life and sexual function. J Cancer Res Ther. 2016;12(2):938-44.

185. Jongpipan J, Charoenkwan K. Sexual function after radical hysterectomy for early-stage cervical cancer. J Sex Med. 2007;4(6):1659-65.

186. Aerts L, Enzlin P, Verhaeghe J, Poppe W, Vergote I, Amant F. Long-term sexual functioning in women after surgical treatment of cervical cancer stages IA to IB: a prospective controlled study. Int J Gynecol Cancer. 2014;24(8):1527-34.

187. Maas CP, ter Kuile MM, Laan E, Tuijnman CC, Weijenborg PT, Trimbos JB, et al. Objective assessment of sexual arousal in women with a history of hysterectomy. BJOG. 2004;111(5):456-62.

188. Roh JW, Lee DO, Suh DH, Lim MC, Seo SS, Chung J, et al. Efficacy and oncologic safety of nerve-sparing radical hysterectomy for cervical cancer: a randomized controlled trial. J Gynecol Oncol. 2015;26(2):90-9.

189. Kim HS, Kim TH, Suh DH, Kim SY, Kim MA, Jeong CW, et al. Success Factors of Laparoscopic Nerve-sparing Radical Hysterectomy for Preserving Bladder Function in Patients with Cervical Cancer: A Protocol-Based Prospective Cohort Study. Ann Surg Oncol. 2015;22(6):1987-95.

190. Lammerink EA, de Bock GH, Pras E, Reyners AK, Mourits MJ. Sexual functioning of cervical cancer survivors: a review with a female perspective. Maturitas. 2012;72(4):296-304.

191. Rosen R, Brown C, Heiman J, Leiblum S, Meston C, Shabsigh R, et al. The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. J Sex Marital Ther. 2000;26(2):191-208.

192. Ryding EL, Blom C. Validation of the Swedish version of the Female Sexual Function Index (FSFI) in women with hypoactive sexual desire disorder. J Sex Med. 2015;12(2):341-9.

193. Pieterse QD, Ter Kuile MM, Maas CP, Kenter GG. The Gynaecologic Leiden Questionnaire: psychometric properties of a self-report questionnaire of sexual function and vaginal changes for gynaecological cancer patients. Psychooncology. 2008;17(7):681-9.

194. Jensen PT, Klee MC, Thranov I, Groenvold M. Validation of a questionnaire for self-assessment of sexual function and vaginal changes after gynaecological cancer. Psychooncology. 2004;13(8):577-92.

195. Laan E, van Driel EM, van Lunsen RH. Genital responsiveness in healthy women with and without sexual arousal disorder. J Sex Med. 2008;5(6):1424-35.

196. Laan E, van Lunsen RH, Everaerd W. The effects of tibolone on vaginal blood flow, sexual desire and arousability in postmenopausal women. Climacteric. 2001;4(1):28-41.

197. Deliganis AV, Maravilla KR, Heiman JR, Carter WO, Garland PA, Peterson BT, et al. Female genitalia: dynamic MR imaging with use of MS-325 initial experiences evaluating female sexual response. Radiology. 2002;225(3):791-9.

198. Kukkonen TM, Binik YM, Amsel R, Carrier S. Thermography as a physiological measure of sexual arousal in both men and women. J Sex Med. 2007;4(1):93-105.

199. Laterza RM, Sievert KD, de Ridder D, Vierhout ME, Haab F, Cardozo L, et al. Bladder function after radical hysterectomy for cervical cancer. Neurourol Urodyn. 2015;34(4):309-15.

200. Plotti F, Angioli R, Zullo MA, Sansone M, Altavilla T, Antonelli E, et al. Update on urodynamic bladder dysfunctions after radical hysterectomy for cervical cancer. Crit Rev Oncol Hematol. 2011;80(2):323-9.

201. Kietpeerakool C, Aue-Aungkul A, Galaal K, Ngamjarus C, Lumbiganon P. Nerve-sparing radical hysterectomy compared to standard radical hysterectomy for women with early stage cervical cancer (stage Ia2 to IIa). Cochrane Database Syst Rev. 2019;2:CD012828.

202. Schafer W, Abrams P, Liao L, Mattiasson A, Pesce F, Spangberg A, et al. Good urodynamic practices: uroflowmetry, filling cystometry, and pressure-flow studies. Neurourol Urodyn. 2002;21(3):261-74.

203. Hofmeester I, Kollen BJ, Steffens MG, Bosch JL, Drake MJ, Weiss JP, et al. Impact of the International Continence Society (ICS) report on the standardisation of terminology in nocturia on the quality of reports on nocturia and nocturnal polyuria: a systematic review. BJU Int. 2015;115(4):520-36.

204. Bergmark K, Avall-Lundqvist E, Dickman PW, Henningsohn L, Steineck G. Patient-rating of distressful symptoms after treatment for early cervical cancer. Acta Obstet Gynecol Scand. 2002;81(5):443-50.

205. Sood AK, Nygaard I, Shahin MS, Sorosky JI, Lutgendorf SK, Rao SS. Anorectal dysfunction after surgical treatment for cervical cancer. J Am Coll Surg. 2002;195(4):513-9.

206. Pieterse QD, Maas CP, ter Kuile MM, Lowik M, van Eijkeren MA, Trimbos JB, et al. An observational longitudinal study to evaluate miction, defecation, and sexual function after radical hysterectomy with pelvic lymphadenectomy for early-stage cervical cancer. Int J Gynecol Cancer. 2006;16(3):1119-29.

207. Sackey H, Johansson H, Sandelin K, Liljegren G, MacLean G, Frisell J, et al. Self-perceived, but not objective lymphoedema is associated with decreased long-term health-related quality of life after breast cancer surgery. Eur J Surg Oncol. 2015;41(4):577-84.

208. Kronenberg H MS, Polnsky K, Reed Larsen P. Williams textbook of Endocrinology. 11 ed.

209. Visser JA, Schipper I, Laven JS, Themmen AP. Anti-Mullerian hormone: an ovarian reserve marker in primary ovarian insufficiency. Nat Rev Endocrinol. 2012;8(6):331-41.

210. La Marca A, Spada E, Grisendi V, Argento C, Papaleo E, Milani S, et al. Normal serum anti-Mullerian hormone levels in the general female population and the relationship with reproductive history. Eur J Obstet Gynecol Reprod Biol. 2012;163(2):180-4.

211. Hallqvist Everhov A, Bergmark K, Smedby KE, Linden Hirschberg A, Floter Radestad A. Anti-Mullerian hormone in premenopausal women following treatment of uterine cervical cancer. Acta Obstet Gynecol Scand. 2014;93(9):949-53.

212. Cameron DR, Braunstein GD. Androgen replacement therapy in women. Fertil Steril. 2004;82(2):273-89.

213. Bui HN, Struys EA, Martens F, de Ronde W, Thienpont LM, Kenemans P, et al. Serum testosterone levels measured by isotope dilution-liquid chromatography-tandem mass spectrometry in postmenopausal women versus those in women who underwent bilateral oophorectomy. Ann Clin Biochem. 2010;47(Pt 3):248-52.

214. Everhov AH, Floter Radestad A, Nyberg T, Smedby KE, Bergmark K, Linden Hirschberg A. Serum Androgen Levels and Sexual Function Before and One Year After Treatment of Uterine Cervical Cancer: A Pilot Study. J Sex Med. 2016;13(3):413-24.

215. Traish AM, Kim N, Min K, Munarriz R, Goldstein I. Role of androgens in female genital sexual arousal: receptor expression, structure, and function. Fertil Steril. 2002;77 Suppl 4:S11-8.

216. Davis S, Papalia MA, Norman RJ, O'Neill S, Redelman M, Williamson M, et al. Safety and efficacy of a testosterone metered-dose transdermal spray for treating decreased sexual satisfaction in premenopausal women: a randomized trial. Ann Intern Med. 2008;148(8):569-77.

217. Davis SR, Worsley R, Miller KK, Parish SJ, Santoro N. Androgens and Female Sexual Function and Dysfunction--Findings From the Fourth International Consultation of Sexual Medicine. J Sex Med. 2016;13(2):168-78.

218. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, et al. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg. 2009;250(2):187-96.

219. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240(2):205-13.

220. Barlow L, Westergren K, Holmberg L, Talback M. The completeness of the Swedish Cancer Register: a sample survey for year 1998. Acta Oncol. 2009;48(1):27-33.

221. Rosenberg P, Kjolhede P, Staf C, Bjurberg M, Borgfeldt C, Dahm-Kahler P, et al. Data quality in the Swedish Quality Register of Gynecologic Cancer - a Swedish Gynecologic Cancer Group (SweGCG) study. Acta Oncol. 2018;57(3):346-53.

222. Sodergard R, Backstrom T, Shanbhag V, Carstensen H. Calculation of free and bound fractions of testosterone and estradiol-17 beta to human plasma proteins at body temperature. J Steroid Biochem. 1982;16(6):801-10.

223. Brookes ST, Donovan JL, Wright M, Jackson S, Abrams P. A scored form of the Bristol Female Lower Urinary Tract Symptoms questionnaire: data from a randomized controlled trial of surgery for women with stress incontinence. Am J Obstet Gynecol. 2004;191(1):73-82.

224. Kelleher CJ, Cardozo LD, Khullar V, Salvatore S. A new questionnaire to assess the quality of life of urinary incontinent women. Br J Obstet Gynaecol. 1997;104(12):1374-9.

225. Lim R, Liong ML, Lim KK, Leong WS, Yuen KH. The Minimum Clinically Important Difference of the International Consultation on Incontinence Questionnaires (ICIQ-UI SF and ICIQ-LUTSqol). Urology. 2019;133:91-5.

226. Jensen MP, Karoly P, Braver S. The measurement of clinical pain intensity: a comparison of six methods. Pain. 1986;27(1):117-26.

227. Abrams P. Bladder outlet obstruction index, bladder contractility index and bladder voiding efficiency: three simple indices to define bladder voiding function. BJU Int. 1999;84(1):14-5.

228. Kaplan E. Nonparametric estimation from incomplete observations. Journal of the American statistical association. 1958;53(282):457-81.

229. Breslow N. Analysis of Survival Data under the Proportional Hazards Model International Statistical Review. 1975;43(1):45-57.

230. Rosenbaum PR DBR. The central role of the propensity score in observational studies for causal effects Biometrika. 1983;70(1):41-55.

231. Raspagliesi F, Bogani G, Pinelli C, Casarin J, Cerrotta AM, Delle Curti CT, et al. Patterns of failure after adjuvant "sandwich" chemo-radio-chemotherapy in locally advanced (stage III-IVA) endometrial cancer. J Cancer Res Clin Oncol. 2020.

232. Hu TWY, Huang Y, Li N, Nie D, Li Z. Comparison of laparoscopic versus open radical hysterectomy in patients with early-stage cervical cancer: a multicenter study in China. Int J Gynecol Cancer. 2020;30(8):1143-50.

233. Paik ES, Lim MC, Kim MH, Kim YH, Song ES, Seong SJ, et al. Comparison of laparoscopic and abdominal radical hysterectomy in early stage cervical cancer patients without adjuvant treatment: Ancillary analysis of a Korean Gynecologic Oncology Group Study (KGOG 1028). Gynecol Oncol. 2019;154(3):547-53.

234. Bogani G, Ghezzi F, Chiva L, Gisone B, Pinelli C, Dell'Acqua A, et al. Patterns of recurrence after laparoscopic versus open abdominal radical hysterectomy in patients with cervical cancer: a propensity-matched analysis. Int J Gynecol Cancer. 2020;30(7):987-92.

235. Jensen PT, Schnack TH, Froding LP, Bjorn SF, Lajer H, Markauskas A, et al. Survival after a nationwide adoption of robotic minimally invasive surgery for early-stage cervical cancer - A population-based study. Eur J Cancer. 2020;128:47-56.

236. Trimbos JB, Hellebrekers BW, Kenter GG, Peters LA, Zwinderman KH. The long learning curve of gynaecological cancer surgery: an argument for centralisation. BJOG. 2000;107(1):19-23.

237. Baeten I, Hoogendam JP, Schreuder H, Jurgenliemk-Schulz IM, Verheijen R, Zweemer RP, et al. The influence of learning curve of robot-assisted laparoscopy on oncological outcomes in early-stage cervical cancer: an observational cohort study. BJOG. 2020.

238. Vickers AJ, Savage CJ, Hruza M, Tuerk I, Koenig P, Martinez-Pineiro L, et al. The surgical learning curve for laparoscopic radical prostatectomy: a retrospective cohort study. Lancet Oncol. 2009;10(5):475-80.

239. Mowat A, Maher C, Ballard E. Surgical outcomes for low-volume vs high-volume surgeons in gynecology surgery: a systematic review and meta-analysis. Am J Obstet Gynecol. 2016;215(1):21-33.

240. Volz J, Koster S, Spacek Z, Paweletz N. The influence of pneumoperitoneum used in laparoscopic surgery on an intraabdominal tumor growth. Cancer. 1999;86(5):770-4.

241. Volz J, Koster S, Weiss M, Schmidt R, Urbaschek R, Melchert F, et al. Pathophysiologic features of a pneumoperitoneum at laparoscopy: a swine model. Am J Obstet Gynecol. 1996;174(1 Pt 1):132-40.

242. Lin F, Pan L, Li L, Li D, Mo L. Effects of a simulated CO2 pneumoperitoneum environment on the proliferation, apoptosis, and metastasis of cervical cancer cells in vitro. Med Sci Monit. 2014;20:2497-503.

243. Kong TW, Chang SJ, Piao X, Paek J, Lee Y, Lee EJ, et al. Patterns of recurrence and survival after abdominal versus laparoscopic/robotic radical hysterectomy in patients with early cervical cancer. J Obstet Gynaecol Res. 2016;42(1):77-86.

244. Kong TW, Son JH, Paek J, Chang SJ, Ryu HS. Prognostic factors influencing pelvic, extra-pelvic, and intraperitoneal recurrences in lymph node-negative early-stage cervical cancer patients following radical hysterectomy. Eur J Obstet Gynecol Reprod Biol. 2020;252:94-9.

245. Kohler C, Hertel H, Herrmann J, Marnitz S, Mallmann P, Favero G, et al. Laparoscopic radical hysterectomy with transvaginal closure of vaginal cuff - a multicenter analysis. Int J Gynecol Cancer. 2019;29(5):845-50.

246. Logani S, Herdman AV, Little JV, Moller KA. Vascular "pseudo invasion" in laparoscopic hysterectomy specimens: a diagnostic pitfall. Am J Surg Pathol. 2008;32(4):560-5.

247. Pedone Anchora L, Turco LC, Bizzarri N, Capozzi VA, Lombisani A, Chiantera V, et al. How to Select Early-Stage Cervical Cancer Patients Still Suitable for Laparoscopic Radical Hysterectomy: a Propensity-Matched Study. Ann Surg Oncol. 2020;27(6):1947-55.

248. Chiva L, Zanagnolo V, Querleu D, Martin-Calvo N, Arevalo-Serrano J, Capilna ME, et al. SUCCOR study: an international European cohort observational study comparing minimally invasive surgery versus open abdominal radical hysterectomy in patients with stage IB1 cervical cancer. Int J Gynecol Cancer. 2020;30(9):1269-77.

249. Lawlor ML, Rao R, Manahan KJ, Geisler JP. Electrosurgical Settings and Vaginal Cuff Complications. JSLS. 2015;19(4).

250. Plotti F, Terranova C, Capriglione S, Crispino S, Li Pomi A, de Cicco Nardone C, et al. Assessment of Quality of Life and Urinary and Sexual Function After Radical Hysterectomy in Long-Term Cervical Cancer Survivors. Int J Gynecol Cancer. 2018;28(4):818-23.

251. Everhov AH, Ekberg S, Hirschberg AL, Bergmark K, Radestad AF, Glimelius I, et al. Lost workdays in uterine cervical cancer survivors compared to the general population: impact of treatment and relapse. J Cancer Surviv. 2016;10(3):514-23.

252. Sjostrom M, Umefjord G, Stenlund H, Carlbring P, Andersson G, Samuelsson E. Internet-based treatment of stress urinary incontinence: a randomised controlled study with focus on pelvic floor muscle training. BJU Int. 2013;112(3):362-72.

253. Coyne KS, Kvasz M, Ireland AM, Milsom I, Kopp ZS, Chapple CR. Urinary incontinence and its relationship to mental health and health-related quality of life in men and women in Sweden, the United Kingdom, and the United States. Eur Urol. 2012;61(1):88-95.

254. Coyne KS, Sexton CC, Irwin DE, Kopp ZS, Kelleher CJ, Milsom I. The impact of overactive bladder, incontinence and other lower urinary tract symptoms on quality of life, work productivity, sexuality and emotional well-being in men and women: results from the EPIC study. BJU Int. 2008;101(11):1388-95.

255. Lee Y, Lim MC, Kim SI, Joo J, Lee DO, Park SY. Comparison of Quality of Life and Sexuality between Cervical Cancer Survivors and Healthy Women. Cancer Res Treat. 2016;48(4):1321-9.

256. Bogani G, Serati M, Nappi R, Cromi A, di Naro E, Ghezzi F. Nerve-sparing approach reduces sexual dysfunction in patients undergoing laparoscopic radical hysterectomy. J Sex Med. 2014;11(12):3012-20.

257. Xue Z, Zhu X, Teng Y. Comparison of Nerve-Sparing Radical Hysterectomy and Radical Hysterectomy: a Systematic Review and Meta-Analysis. Cell Physiol Biochem. 2016;38(5):1841-50.

258. Bakker RM, Pieterse QD, van Lonkhuijzen L, Trimbos B, Creutzberg CL, Kenter GG, et al. A Controlled Study on Vaginal Blood Flow During Sexual Arousal Among Early-Stage Cervical Cancer Survivors Treated With Conventional Radical or Nerve-Sparing Surgery With or Without Radiotherapy. Int J Gynecol Cancer. 2017;27(5):1051-7.

259. Tsatsou I, Parpa E, Tsilika E, Katsaragakis S, Batistaki C, Dimitriadou E, et al. A Systematic Review of Sexuality and Depression of Cervical Cancer Patients. J Sex Marital Ther. 2019;45(8):739-54.

260. Jeppesen MM, Mogensen O, Dehn P, Jensen PT. Needs and priorities of women with endometrial and cervical cancer. J Psychosom Obstet Gynaecol. 2015;36(3):122-32.

261. Davis SR, van der Mooren MJ, van Lunsen RH, Lopes P, Ribot C, Rees M, et al. Efficacy and safety of a testosterone patch for the treatment of hypoactive sexual desire disorder in surgically menopausal women: a randomized, placebo-controlled trial. Menopause. 2006;13(3):387-96.

262. Kissell KA, Danaher MR, Schisterman EF, Wactawski-Wende J, Ahrens KA, Schliep K, et al. Biological variability in serum anti-Mullerian hormone throughout the menstrual cycle in ovulatory and sporadic anovulatory cycles in eumenorrheic women. Hum Reprod. 2014;29(8):1764-72.

263. Salonia A, Pontillo M, Nappi RE, Zanni G, Fabbri F, Scavini M, et al. Menstrual cycle-related changes in circulating androgens in healthy women with self-reported normal sexual function. J Sex Med. 2008;5(4):854-63.

264. van Disseldorp J, Lambalk CB, Kwee J, Looman CW, Eijkemans MJ, Fauser BC, et al. Comparison of inter- and intra-cycle variability of anti-Mullerian hormone and antral follicle counts. Hum Reprod. 2010;25(1):221-7.

265. Burger HG. Androgen production in women. Fertil Steril. 2002;77 Suppl 4:S3-5.

266. Khajehei M, Doherty M, Tilley PJ. An update on sexual function and dysfunction in women. Arch Womens Ment Health. 2015;18(3):423-33.