

Laparoscopic radical hysterectomy with transvaginal closure of vaginal cuff – a multicenter analysis

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HIGHLIGHTS

- Vaginally-assisted laparoscopic radical hysterectomy was oncologically safe in patients with early cervical cancer in a retrospective analysis.
- Vaginally-assisted laparoscopic radical hysterectomy avoids the use of a manipulator and potentially prevents tumor spillage.
- Oncologic outcomes of combined vaginal-laparoscopic radical hysterectomy are similar to those of open radical hysterectomy in the LACC trial.

ABSTRACT

Objective Laparoscopic/robotic radical hysterectomy has been historically considered oncologically equivalent to open radical hysterectomy for patients with early cervical cancer. However, a recent prospective randomized trial (Laparoscopic Approach to Cervical Cancer, LACC) has demonstrated significant inferiority of the minimally invasive approach. The aim of this study is to evaluate the oncologic outcomes of combined laparoscopic-vaginal radical hysterectomy.

Methods Between August 1994 and December 2018, patients with invasive cervical cancer were treated using minimally-invasive surgery at the Universities of Jena, Charité Berlin (Campus CCM and CBF) and Cologne and Asklepios Clinic Hamburg. 389 patients with inclusion criteria identical to the LACC trial were identified. In contrast to the laparoscopic/robotic technique used in the LACC trial, all patients in our cohort underwent a combined transvaginal-laparoscopic approach without the use of any uterine manipulator.

Results A total of 1952 consecutive patients with cervical cancer were included in the analysis. Initial International Federation of Gynecology and Obstetrics (FIGO) stage was IA1 lymphovascular space invasion (LVSI+), IA2 and IB1/IIA1 in 32 (8%), 43 (11%), and 314 (81%) patients, respectively, and histology was squamous cell in 263 (68%), adenocarcinoma in 117 (30%), and adenosquamous in 9 (2%) patients. Lymphovascular invasion was confirmed in 106 (27%) patients. The median number of lymph nodes was 24 (range 2–86). Lymph nodes were tumor-free in 379 (97%) patients. Following radical hysterectomy, 71 (18%) patients underwent adjuvant chemoradiation or radiation. After a median follow-up of 99 (range 1–288) months, the 3-, 4.5-, and 10-year disease-free survival rates were 96.8%, 95.8%, and 93.1%, and the 3-, 4.5-, and 10-year overall survival rates were 98.5%, 97.8%, and 95.8%, respectively. Recurrence location was loco-regional in 50% of cases with recurrence (n=10). Interestingly, 9/20 recurrences occurred more than 39 months after surgery.

Conclusion The combined laparoscopic-vaginal technique for radical hysterectomy with avoidance of spillage and manipulation of tumor cells provides excellent oncologic outcome for patients with early cervical cancer. Our retrospective data suggest that laparoscopic-vaginal surgery may be oncologically safe and should be validated in further randomized trials.

INTRODUCTION

The best surgical approach for patients with early stage cervical cancer has been a matter of debate since Schauta's and Wertheim's era.^{1,2} With the ability of safe and oncologically adequate performance of laparoscopic pelvic/para-aortic lymphadenectomy³ the way was paved for laparoscopic radical hysterectomy as an alternative to open radical hysterectomy. The initial technique of laparoscopic assisted radical vaginal hysterectomy⁴ has never been widely adopted due to a long learning curve and an increased risk of urologic complications. Thus, total laparoscopic or robotic-assisted radical hysterectomy became the most often used techniques of minimally invasive radical hysterectomy.^{5–7} Meta-analyses, including retrospective data comparing open and laparoscopic radical hysterectomy, show no significant difference in oncologic outcome (disease-free survival 85–95% and overall survival 93–97%) with less peri- and post-operative morbidity for the minimally invasive technique.^{8–11} Consequently, the minimally invasive approach was firmly established in guidelines (National Comprehensive Cancer Network (NCCN), European Society of Gynaecological Oncology (ESGO)) as a valid alternative to open radical hysterectomy.^{12,13}

Techniques of minimally invasive radical hysterectomy (total laparoscopic as well as robotic-assisted radical hysterectomy) are almost always

associated with the use of uterine manipulators.⁵⁻⁷ Moreover, in these approaches, following parametrial resection, the vaginal cuff is opened laparoscopically above the manipulator rim and, thus, tumor cells may be spread within the peritoneal cavity by circulating carbon dioxide. Basic principles of oncologic surgery are careful tumor manipulation, resection in tumor-free margins, and avoidance of tumor spillage. We have established a surgical technique combining a laparoscopic and vaginal approach,^{4 14} where we refrain from using a uterine manipulator and always create a tumor-covering vaginal cuff transvaginally.

In the Laparoscopic Approach to Cervical Cancer (LACC) trial, the investigators found a significant oncologic inferiority (disease-free survival, pelvic recurrences) of minimally invasive radical hysterectomy compared with open radical hysterectomy.¹⁵ Despite surprising results, Ramirez et al are to be credited for having performed the first randomized trial comparing these two surgical approaches and thereby producing better evidence for best treatment of women with early cervical cancer.¹⁵ It is also a trigger for gynecologic surgeons to call their technique of radical hysterectomy and its results into question.

In the current retrospective cohort study we have updated our prospective database of all consecutive patients with initial International Federation of Gynecology and Obstetrics (FIGO) stages identical to LACC who were treated by combined vaginal-laparoscopic radical hysterectomy with respect to disease-free survival and overall survival.

METHODS

Our prospective database of 1952 consecutive women diagnosed with invasive cervical cancer and treated surgically by our group between August 1994 and December 2018 was analyzed with respect to inclusion criteria identical to those in LACC. A total of 389 patients were identified and all underwent combined laparoscopic-vaginal radical hysterectomy with sentinel mapping and lymphadenectomy or complete pelvic lymphadenectomy (within Uterus III study, Aptima study, laparoscopic assisted radical vaginal hysterectomy (LARVH) study or ongoing SENTIX trial) at the University of Jena (1994–2004), Charité University Berlin Campus Mitte and Campus Benjamin Franklin (2004–2013), University of Cologne, and Asklepios Clinic Hamburg (2014–2018). Selection bias is excluded since not a single patient with early stage disease underwent open surgery.

From 1994 to 2005 we have used the technique of laparoscopic assisted radical vaginal hysterectomy for combined laparoscopic-vaginal radical hysterectomy with predominant vaginal resection of parametria. Despite encouraging oncologic results,¹⁶ we had to modify this approach due to a peri- and post-operative urologic complication rate of >10% and difficulty in passing the learning curve. From 2005 up to now the technique of vaginal-assisted laparoscopic radical hysterectomy¹⁴ has been used. Both techniques have already been described in detail.^{4 14} In both techniques the vaginal creation of a tumor covering vaginal cuff and the strict avoidance of use of any uterine manipulator is mandatory. The key differences of vaginal-assisted laparoscopic radical hysterectomy compared with standard minimally invasive radical hysterectomy are shown in Figure 1 and Figure 2. In accordance with guidelines

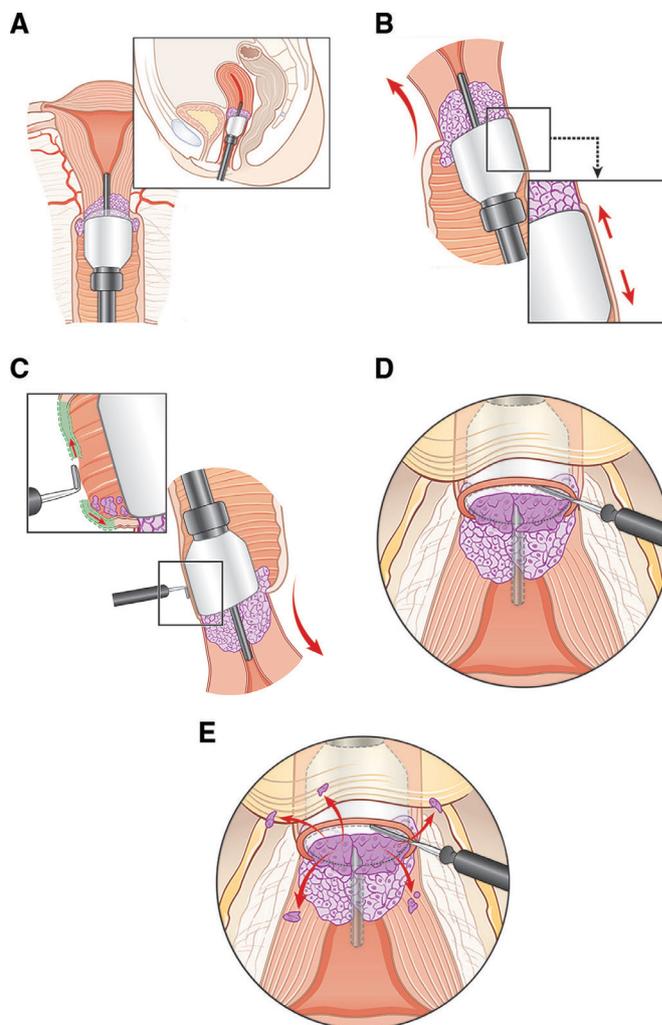


Figure 1 (A-E). Selected surgical steps of total laparoscopic radical hysterectomy/robotic radical hysterectomy (TLRH/RRH). (A) Transtumoral placement of uterine manipulator (tumor cells = purple). (B) Movement of the transtumoral uterus manipulator stretches the vagina and potentially mobilizes the tumor cells. (C) After laparoscopic/robotic cutting of the stretched vagina over the manipulator's rim using a monopolar hook, the vagina immediately retracts. Thus, a vaginal gap is created and the peritoneal cavity and vagina are connected. (D, E) Via the vaginal-peritoneal connection, tumor cells can be distributed into the peritoneal cavity by circulating carbon dioxide.

(ESGO) to avoid combined morbidity of radical hysterectomy and adjuvant chemoradiation, surgery has always been abandoned in patients with positive lymph nodes on frozen section, and primary chemoradiation or radiotherapy performed.¹⁷

Patient follow-up was updated in the third and fourth quarter of 2018 using questionnaires and phone calls (online supplementary file 1). All patients, even the few who were not treated within an ongoing study at the time of surgery, gave their consent. This is an uncontrolled single arm study to evaluate the outcome of combined vaginal-laparoscopic radical hysterectomy in a large multicenter cohort. Progression-free and overall survival was estimated using the Kaplan-Meier method. Additionally, two-sided 95% confidence intervals (95% CI) were obtained for progression-free and overall

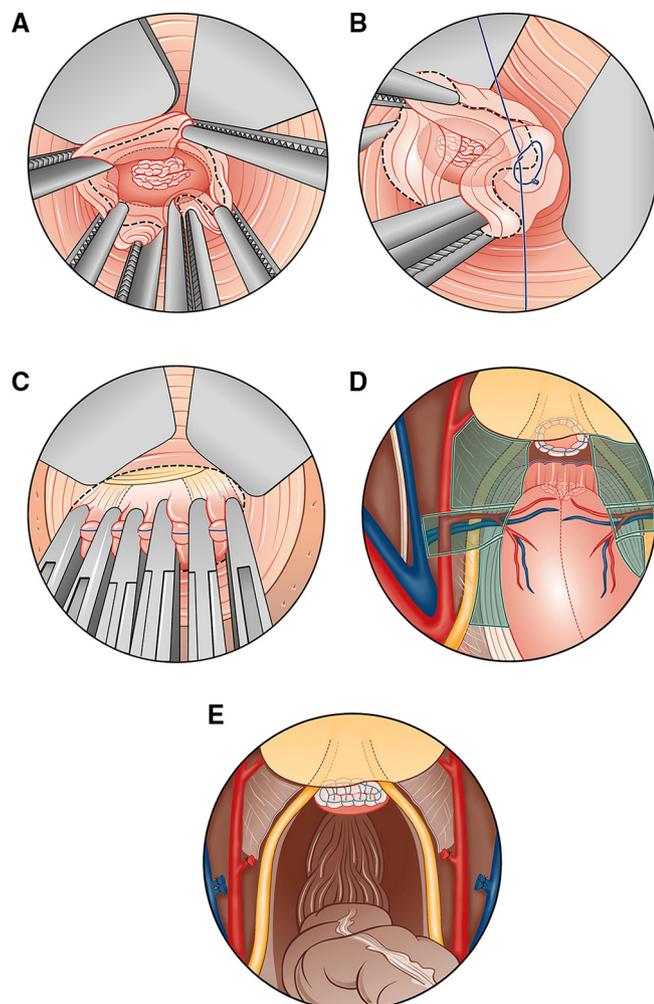


Figure 2 (A-E) Selected surgical steps of vaginal-assisted laparoscopic radical hysterectomy (VALRH). (A) Vaginal creation of the vaginal cuff in iodine-positive area using 6 straight Kocher clamps. (B) Closing of the vaginal cuff by continuous suture. (C) Grasping the closed vaginal cuff using serrated clamps to open the cul-de-sac and vesico-vaginal space. (D) Extension of laparoscopic parametrial resection (green areas) following transvaginal creation and closure of the vaginal cuff. (E) Final laparoscopic situs after VALRH.

survival after 3 years and for progression-free survival after 10 years using the formula of Greenwood. Median follow-up was determined coding events as censored and censored cases as events in a Kaplan-Meier analysis. No significance tests were performed. All statistical analyses were done using Statistical Package for the Social Sciences release 24.

RESULTS

Within the study period, 389 patients with early cervical cancer underwent laparoscopic-assisted radical vaginal hysterectomy or vaginal-assisted laparoscopic radical hysterectomy in combination with pelvic lymphadenectomy. There was no conversion to laparotomy necessary in any patient. The median age of patients was 43 (range 17–81) years (Table 1). Histology resulted in squamous cell in 263 (68%) patients, adenocarcinoma in 117 (30%) patients, and adenosquamous tumor in 9 (2%) patients. Tumor grading 1, 2

Table 1 Patient characteristics

n=389	
Median age (years)	43 (17–81)
Histology	Squamous: 263 (68%) Adeno: 117 (30%) Adenosquamous: 9 (2%)
Stage (TNM)	IA1 LVSI: 32 (8%) IA2: 43 (11%) IB1: 312 (80%) IIA1: 2 (1%)
Tumor size	≤2 cm: 253 (65%) >2cm: 136 (35%)
Conversion to laparotomy	0
Grading	1 49 (13%) 2 228 (58%) 3 112 (29%)
Parametrial involvement	2 (1%)
Vaginal involvement	1
LVSI	Negative 283 (73%), Positive 106 (27%)
Number of lymph nodes (median)	24 (2–86)
Histology lymph nodes	Tumor free: 379 (97%), Tumor involved: 10 (3%)
Adjuvant RCTX/radiotherapy	No 318 (82%), Yes 71 (18%)

LVSI, lymphovascular space invasion; RCTX, radio-chemotherapy.

and 3 was found in 49 (13%), 228 (58%), and 112 (29%) patients, respectively. Lymphovascular invasion was confirmed in 106 (27%) patients. Distribution of TNM stages was IA1 LVSI+, IA2, IB1, and IIA1 in 32 (8%), 43 (11%), 312 (80%), and 2 (1%) patients, respectively. Maximum tumor size ≤2 cm was diagnosed in 253 (65%) patients and >2 cm in 136 (35%) patients. The median number of lymph nodes was 24 (range 2–86) despite the fact that 23 (6%) of patients exclusively underwent pelvic sentinel lymphadenectomy within two trials (Uterus III of German Cancer Association and ongoing SENTIX trial). Histologically, lymph nodes were tumor-free in 379 (97%) patients and with evidence of metastatic disease in 10 (3%) patients. Microscopic parametrial spread was detected in two patients and vaginal involvement in one patient. Following radical hysterectomy 71 (18%) patients underwent adjuvant chemo-radiation or radiotherapy.

Follow-up data are available from all patients and are current for the fourth quarter of 2018, with the exception of six (1.5%) patients. Of these six patients follow-up data of at least 5 years' duration are available. After a median follow-up of 99 (range 1–288) months, 3-, 4.5-, and 10-year disease-free survival rates are 96.8%, 95.8%, and 93.1%, and 3-, 4.5-, and 10-year overall survival percentages are 98.5%, 97.8%, and 95.8%, respectively (Table 2). In 10 patients (50%) recurrences were loco-regional, whereas in the other 10 (50%) patients distant metastases were diagnosed (online supplementary table 1). Interestingly, nine of 20 recurrences occurred after 3 years (detected 39, 42, 48, 63, 69, 75, 87, 105, and 108 months after surgery).

Table 2 Comparison of disease-free survival and overall survival between LACC and this study

DFS	Follow-up	3 years DFS	4.5 years DFS	5 years DFS	10 years DFS
		No. at risk (%)			
LSC/robot arm in LACC trial	2.5 years	87.1% 142 (45%)	86% 80 (25%)	n/a 5 (2%)	n/a
Laparotomy arm in LACC trial	2.5 years	97.1% 134 (43%)	96.5% 90 (29%)	n/a 7 (2%)	n/a
Own results	>8 years (99 months)	96.8% 305 (78%)	95.8% 271 (70%)	95.7% 264 (68%)	93.1% 138 (35%)
OS	Follow-up	3 years OS	4.5 years OS	5 years OS	10 years OS
		No. at risk (%)			
LSC/robot arm in LACC trial	2.5 years	93.8% 150 (47%)	n/a 87 (27%)	n/a 5 (2%)	n/a
Laparotomy arm in LACC trial	2.5 years	99% 136 (44%)	n/a 90 (29%)	n/a 7 (2%)	n/a
Own results	>8 years (99 months)	98.5% 306 (78%)	97.8% 273 (70%)	97.6% 265 (68%)	95.8% 138 (35%)

DFS, disease-free survival; LACC, Laparoscopic Approach to Cervical Cancer; OS, overall survival.

DISCUSSION

Radical hysterectomy is the standard surgical treatment for patients diagnosed with early cervical cancer.^{12,13} Historically radical vaginal hysterectomy was abandoned at the beginning of the last century since it did not allow the removal of regional lymph nodes, the most common site of metastases in cervical cancer patients.¹ With the introduction of laparoscopic lymphadenectomy, lymph node harvesting became possible and thus transvaginal approach for radical hysterectomy and trachelectomy was revived, combining the advantages of a transabdominal and transvaginal approach.³ The benefits of minimal invasive surgery with respect to the patient's quality of life became evident and an increasing number of gynecologic oncologists switched to this technique. However, since transvaginal surgery is not taught in the majority of gynecologic oncology fellowship programs an exclusive laparoscopic or robotic approach was introduced, thus eliminating the vaginal part of the technique.^{5-11, 18-26} Several randomized trials in patients with endometrial cancer showed equivalent results in terms of disease-free and overall survival in patients treated minimally-invasively compared with open surgery. The advantages of minimal invasive surgery include shorter hospital stay, less use of analgesics, lower rate of complications, and improved quality of life.²⁷

For patients diagnosed with early cervical cancer, the identical advantages of minimally-invasive radical hysterectomy have been demonstrated in many mono- or multicentered studies.^{5, 8, 18, 19} However, the surgical anatomy and biology of endometrial and cervical cancer differ considerably. In particular, the risk of contaminating the small pelvis with tumor cells is considerably higher in cervical cancer patients when the tumor is manipulated by instruments and brought into contact with the pelvic peritoneum.

Published techniques of total laparoscopic radical hysterectomy (TLRH) and robotic radical hysterectomy (RRH) include almost always use of a uterine manipulator, even in patients with visible tumor, and therefore violate the basic principles of oncologic surgery such as gentle tumor manipulation, resection in tumor-free margins, and avoidance of tumor spillage. Additionally, exposing the

tumor to circulating carbon dioxide can lead to loco-regional tumor implants.²⁸ Despite some reservations regarding manipulator application,²⁹ it has been widely used and considered safe among most gynecologic oncologists.^{6,30} In contrast, our group has established a surgical technique combining a laparoscopic and vaginal approach,¹⁴ in which we never used any uterine manipulator and always created a tumor-covering vaginal cuff transvaginally.

Until the end of 2018 minimally-invasive as well as open approaches had been accepted as safe and oncologically adequate surgery for radical hysterectomy (NCCN, ESGO) on the basis of large meta-analyses and/or non-randomized prospective or retrospective studies.^{8-11, 20-26}

The publication of the first randomized trial comparing minimally invasive versus open radical hysterectomy by Ramirez et al has raised many questions and caused uncertainties.¹⁵ In the LACC trial, 319 patients diagnosed with early cervical cancer were treated by total laparoscopic or robotic radical hysterectomy of whom 27 experienced recurrence or death from cancer; 66% of recurrences were loco-regional with a median follow-up of 2.5 years. The study was prematurely closed by the safety monitoring committee due to significant inferiority of the minimally invasive arm.

The unexpected results of the LACC trial have been discussed in many editorials focusing on several aspects of radical hysterectomy such as the learning curve, vaginal cuff length, radicality of parametrial resection, ethnic differences, extent of lymphadenectomy, and standardization of surgery, but also this has given rise to very emotional factors, with personal editorials, such as the best surgical school, and comparability of centers and surgical skills.^{31,32} Even in the knowledge of two smaller randomized trials focusing on the radicality of parametrial resection,^{33,34} the LACC trial gave rise to a new discussion about oncologic safety of various surgical approaches for radical hysterectomy, and demonstrated improved oncologic outcome of open radical hysterectomy with disease-free survival of 97.1% and overall survival of 99% after 3 years.

Our study population comprises 389 patients, compared with 319 patients in the minimally invasive arm of the LACC trial, with

nearly identical tumor characteristics. No surgery in our study had to be converted to an open approach in comparison to 3.5% in the LACC trial. The considerably lower percentage of lymph node positivity in our cohort (3% vs 12.4%) is caused by our treatment strategy to abandon radical hysterectomy in patients with proven lymph node positivity on frozen section at the beginning of surgery.^{17,35} This is well balanced with the 11% lower rate of adjuvant radiochemotherapy and radiation in our cohort of patients. The major difference between the minimally invasive arm in the LACC trial and our cohort is the surgical technique used, with strict avoidance of tumor manipulation and tumor cell contamination of the peritoneal cavity.

In our retrospective study of 389 consecutive patients with initial FIGO stages identical to the LACC trial and a median follow-up period of >8 years, 3-year overall survival and 3-year disease-free survival are 98.5% and 96.8%, respectively. Besides oncologic results, the follow-up interval in patients with cervical cancer has to be newly defined, looking at our data where almost half of the recurrences occurred after more than 3 years.

Our study has several advantages and drawbacks. The major weakness is its non-randomized design. However, compared to the laparoscopic arm of the LACC trial, our retrospective multicenter study comprises a larger number of patients with early cervical cancer who underwent a standardised technique of combined laparoscopic-vaginal radical hysterectomy without the use of a uterine manipulator and laparoscopic opening of the vagina. The gynecologic surgeons in each center were trained under the same surgical school and underwent several years of supervised training. Therefore a homogeneous performance of surgery is very likely. Oncologic data in our study are based on a median follow-up of >8 years in comparison to 2.5 years in the LACC trial. Data completeness is nearly 100% compared with 60% in the LACC trial.

In conclusion, our oncologic data of 389 patients treated by laparoscopic-assisted radical vaginal hysterectomy or vaginal-assisted laparoscopic radical hysterectomy are nearly identical to the excellent results of open radical hysterectomy in the LACC trial. Our results call for a new prospective randomized trial comparing vaginal-assisted laparoscopic radical hysterectomy with open radical hysterectomy.

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