

Surgical treatment of endometrioid endometrial carcinoma - laparotomy versus laparoscopy

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Abstract

Objective: Recent publications have raised doubts about the oncological safety of a laparoscopic approach in the treatment of endometrial cancer. The aim of this study was to investigate the beneficial aspects of laparoscopy versus laparotomy in patients with endometrial cancer, and present oncological outcomes.

Material and Methods: A retrospective study of patients who underwent surgery for the treatment of endometrioid endometrial cancer was performed. Surgical outcomes and complications in patients who were treated by laparoscopy or open surgery were compared. The patients were followed for 5-years. Patients' characteristics, tumor stage, complications rate and oncologic outcome were analyzed.

Results: A total of 151 patients were included. The laparoscopy (n=80) and laparotomy (n=71) groups were homogeneous in regards of demographic data and tumor stage. Median average blood loss (1.31 vs. 1.92 g/dL), the mean duration of hospitalization (5.73 vs. 12.25 days), intraoperative (0 vs. 6%), and severe postoperative complications (5.1 vs. 14.3%) were significantly lower in the laparoscopy group. The numbers of pelvic or para-aortic lymph nodes removed during systematic lymphadenectomy were similar in both groups. Women who underwent laparoscopy and those who underwent laparotomy had similar five-year recurrence-free survival rates (88.7% vs. 91.5%, p=0.864), as well as similar overall five-year survival rates (91.2% vs. 97.2%, p=0.094).

Conclusion: The oncological outcome of laparoscopy was similar to that of laparotomy in the treatment of patients with endometrial cancer. However, surgical outcomes and morbidity rates were significantly better in patients treated by laparoscopy. Clinical trials are essential to evaluate the oncological efficacy of laparoscopy in patients with endometrial cancer. (J Turk Ger Gynecol Assoc 2022; 23: 233-40)

Keywords: Endometrial cancer, laparotomy, laparoscopy, complications, oncological outcome

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Introduction

Endometrial carcinoma is the most common cancer of the female genital organs and the fourth most common malignant disease in women (1). As endometrial carcinoma is frequently accompanied by the early symptom of vaginal bleeding, the disease is diagnosed in an early stage in more than 75% of patients (2,3). This explains the favorable

prognosis of the disease, which accounts for no more than 2.5 % of all cancer-related deaths, with five-year survival rates reported to range from 80% to 85% (1). However, due to the increasing number of women over the age of 60 years in the general population, the incidence of the disease is expected to rise (4). The disease rate is expected to increase by 1-2% every year, which makes this type of cancer a matter of concern for gynecologists (1).



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Surgery is the primary treatment for patients with early endometrial cancer (5). Various studies have shown that the advantages of laparoscopic surgery over open surgery include a lower rate of postoperative adhesions, a shorter hospital stay, fewer postoperative complications, less pain, and better quality of life due to faster recovery (6-11). Furthermore, several studies have concluded that minimally invasive surgery provides similar oncological outcomes and is associated with lesser morbidity compared to laparotomy (12,13). Minimally invasive surgery was included in the majority of the existing guidelines throughout the world for the treatment of endometrial cancer (14,15). Given the option of the laparoscopic approach, primary surgery is performed by laparoscopy in the large majority of hospitals. However, minimally invasive treatment of malignant diseases, such as cervical cancer, has been controversial in the last few years (16). A randomized international multicenter study on cervical cancer published by Ramirez and co-workers revealed that radical endoscopic surgery was associated with a significantly higher risk of recurrence and mortality compared to the open procedure (16). Despite the numerous explanations offered for this phenomenon, including the use of a uterine manipulator and the method of colpotomy, the reasons for the unfavorable effects of the minimally invasive approach are not clear. Tumor exposure may be a likely reason for high recurrence rates after minimally invasive surgery.

Knowledge of the exact factors that worsen the outcome is of utmost importance in order to devise innovative programs that will overcome these obstacles and provide all benefits of minimally invasive surgery for comprehensive and sustainable treatment of cancer patients. Until this problem has been solved, we may need to take a step backward in oncologic surgery and review the surgical access for endometrial cancer. In our department patients with endometrioid endometrial cancer were treated by either a laparoscopic procedure or open surgery. The aims of the investigation were to determine the advantages and disadvantages of both surgical approaches in terms of oncological safety and surgical outcome.

Material and Methods

At a single tertiary university center, a retrospective analysis of patients with histologically confirmed endometrioid endometrial cancer, presenting from 2006 to 2016, was performed. Using the hospital information system, the patients' medical records were collected and analysed. Data collected included intra- and post-operative parameters, such as complication rates, the radicality of lymphadenectomy, blood loss, the duration of surgery and the duration of hospitalization, for all patients with endometrioid endometrial cancer, treated by the laparoscopic procedure or open surgery. The five-year oncological outcome was analyzed.

Patients without well documented histopathological results were excluded. Intra- and post-operative data, as well as clinical parameters were analyzed. The majority of operations until 2010 were performed by the open approach. Laparoscopic access was used on a standard basis after this time. Patients were divided by technique into those that underwent surgery by laparoscopy [laparoscopy group = (LSC group)], and those patients operated by laparotomy [laparotomy group = (LAP group)]. The study was in compliance with the Helsinki Declaration and was approved by the Ethics Committee of the University of Luebeck (approval number: 18-229A, date: 16.08.2018). Informed consent was obtained. Patients with primary metastasis or International Federation of Gynecology and Obstetrics (FIGO) stage 4 disease, or cancer of non-endometrioid histology, such as a serous or clear cell carcinoma, or patients with incomplete resection (R1), were not included in the study.

All patients underwent hysterectomy and bilateral adnectomy. Depending on tumor stage, peritoneal biopsies or pelvic and para-aortic lymphadenectomy were performed. Frozen sections were used to estimate the depth of myometrial invasion intraoperatively. Pelvic and para-aortic lymphadenectomy was performed in cases of myometrial invasion of 50% or more (17,18). The uterus was sent to an experienced pathologist and evaluated both macroscopically and microscopically. Cancer was categorized according to the FIGO staging system. In keeping with our clinical protocols, which concur with the German guidelines (17), patients were given a single-shot intravenous antibiotic intra-operatively and low-dose heparin post-operatively.

A pre-operative score was used to assess the risk of the surgical access due to previous operations. One point was assigned for each laparoscopy in the patient's medical history, and two points for each laparotomy, whether transverse or longitudinal. Postoperative complications were classified according to the Clavien-Dindo classification (19). Grade 1 and 2 complications were rated mild, and grades 3-5 complications severe. Postoperative complications were recorded until one month after the operation. Patients were followed up for at least five years postoperatively on the basis of the hospital information system or by letter. Follow-up data included the location of recurrence, recurrence-free survival rates, and overall survival rates. Local recurrence was defined as disease in the vaginal vault or lesser pelvis, whereas distant metastasis included disease in the lungs, lymph nodes, or liver.

Statistical analysis

Statistical analysis was performed by IBM SPSS Statistics for Windows, version 21.0 (IBM Inc., Armonk, NY, USA). Qualitative variables were described by frequency (percentage) and

compared between groups using the chi-square test or Fisher's exact test, as appropriate. Normal distribution of data was assessed using a one-sample Kolmogorov-Smirnov test. Quantitative variables were expressed as the mean and standard deviation or median. The Mann-Whitney U test and Student's t-test were also used. P-values less than or equal to 0.05 were considered statistically significant.

Results

There were a total of 151 cases, of which 80 patients were included in the LSC group and 71 patients were included in the LAP group. The mean age of patients in the LSC and LAP groups were 63.75 ± 12 years and 64.93 ± 13 years, respectively ($p=0.633$). The groups did not differ significantly in terms of their physical constitution or American Society of Anesthesiology (ASA) classification. Sociodemographic parameters are presented in Table 1. The applied pre-operative score yielded no significant difference between groups in the number of previous abdominal procedures.

Intra-operative parameters are shown in Table 2. Pelvic lymphadenectomy was performed in 42 patients in the LSC group and 46 patients in the LAP group. The mean duration of the operation was 171.48 ± 94 minutes in the LSC group and 176.32 ± 84 minutes in the LAP group ($p=0.335$). Median blood loss, measured by the difference between pre- and

post-operative hemoglobin (Hb) levels, differed significantly between the groups (Table 2). Mean blood loss was 121.3 mL in the LSC group and 286.4 mL in the LAP group ($p<0.001$). Injuries to intra-abdominal organs occurred exclusively in the LAP group; these consisted of three perforations of the bladder and one injury to the small bowel.

As shown in Table 2, the groups were homogeneous in regard of tumor stage. The majority of patients were operated on at FIGO stage 1 in both groups (80% in the LSC group and 73.2% in the LAP group). Cancer grades did not differ significantly between groups: a little more than 60% of the cancers were grade 1 tumors in both groups. On average, 16.2 ± 11 pelvic lymph nodes were removed by laparoscopy and 18.1 ± 14 by laparotomy ($p=0.092$). Furthermore, 12.5 ± 8 para-aortic lymph nodes were removed by laparoscopy and 12.1 ± 5.4 lymph nodes by laparotomy ($p=0.510$). Positive pelvic lymph nodes were found in seven (8.75%) patients who underwent laparoscopic surgery and six (8.45%) who underwent open surgery ($p=0.484$).

Postoperative data are shown in Table 3. Patients in the LSC group were hospitalized on average 5.73 days postoperatively. In comparison, patients who underwent laparotomy were hospitalized for 12.25 days after the operation ($p<0.001$). According to the Clavien-Dindo classification, significantly more grade 3b complications occurred in the LAP group (10%; $n=7$)

Table 1. Demographic data and surgery groups

Parameters	LAP (n=71)	LSC (n=80)	Total	p-value
Age (years)	64.93 ± 13.28	63.75 ± 12.52	64.30 ± 12.86	0.673 [†]
BMI (kg/m ²)	29.7319 ± 6.33	30.6538 ± 9.23	30.2245 ± 8.00	0.978 [†]
ASA I	10 (14.5%)	4 (5.1%)	14 (9.5%)	0.051 ^{††}
ASA II	31 (44.9%)	41 (51.9%)	72 (48.6%)	0.397 ^{††}
ASA III	27 (39.1%)	33 (41.8%)	60 (40.5%)	0.744 ^{††}
ASA IV	1 (1.4%)	1 (1.3%)	2 (1.4%)	1.000 ^{†††}
Mean no. of pregnancies	2.19 ± 1.66	1.62 ± 1.27	1.89 ± 1.49	0.046 [†]
Mean no. of births	1.86 ± 1.45	1.44 ± 1.22	1.64 ± 1.35	0.091 [†]
Premenopausal	12 (16.9%)	12 (15.2%)	24 (16.0%)	0.775 ^{††}
Postmenopausal	59 (83.1%)	67 (84.8%)	126 (84.0%)	0.775 ^{††}
Smoking	15 (21.4%)	15 (20.0%)	30 (20.7%)	0.832 ^{††}
Pre-operative score 6	2 (2.8%)	0 (0.0%)	2 (1.3%)	0.219 ^{†††}
Pre-operative score 5	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Pre-operative score 4	2 (2.8%)	4 (5.0%)	6 (4.0%)	0.685 ^{†††}
Pre-operative score 3	1 (1.4%)	3 (3.8%)	4 (2.6%)	0.623 ^{†††}
Pre-operative score 2	5 (7.0%)	6 (7.5%)	11 (7.3%)	0.914 ^{††}
Pre-operative score 1	5 (7.0%)	14 (17.5%)	19 (12.6%)	0.053 ^{††}
Pre-operative score 0	56 (78.9%)	53 (66.3%)	109 (72.2%)	0.084 ^{††}

(n) indicates the number of patients in each subgroup who reported for evaluation.

LAP: Laparotomy group, LSC: Laparoscopy group, BMI: Body mass index, ASA: American Society of Anesthesiologists Physical Class System, [†]Mann-Whitney U test, ^{††}chi-square test, ^{†††}Fisher's exact test

than in the LSC group (0%; n=0) (p=0.004). More numerous high-grade complications (grades 3a to 5) occurred in patients of the LAP group compared to the LSC group (p=0.045).

The LSC and LAP groups had similar five-year disease-free survival rates (88.7% vs. 91.5%, respectively). Disease recurrence was noted in nine patients in the LSC group and six patients in the LAP group (Figure 1). Local recurrence was observed in five patients (four in the LSC group and one in the LAP group), whereas distant metastases were registered in two patients (0 in the LSC group and two in LAP group). The remaining patients had both local and distant disease recurrence. The

five-year survival rate did not differ significantly: 91.2% vs. 97.2% in the LSC and LAP groups, respectively. Seven patients in the LSC group and two in the LAP group died. Adjuvant therapy (radiation with or without chemotherapy) was applied to a similar extent in both groups. Median disease-free survival was 14.83±11 months in the LSC group and 15.33±5 months in the LAP group; overall survival rates were 25.00±15 and 32.00±30 months, respectively.

Discussion

The treatment of endometrioid endometrial cancer by the laparoscopic approach is associated with fewer intraoperative and postoperative complications than treatment by open surgery. Blood loss was significantly lower and the duration of hospitalization shorter in the laparoscopic group. Five-year disease-free survival rates and overall five-year survival rates were similar in both groups.

The laparoscopic approach is used to an increasing extent, especially in early stages of cancer. Tumor stage and lymphadenectomy rates were similar in both groups. The published literature reports more frequent use of open surgery than laparoscopy in patients with higher FIGO stages of disease (20-22). According to international data, minimally invasive surgery has been performed in 1.88-4.75% of patients with FIGO stage 3A, and in 0-1.54% of patients with FIGO stage 3B disease (21,23). These rates are somewhat lower than those registered in the present study (8.8%). The mean age and body mass index of our patients are in line with published data for endometrial

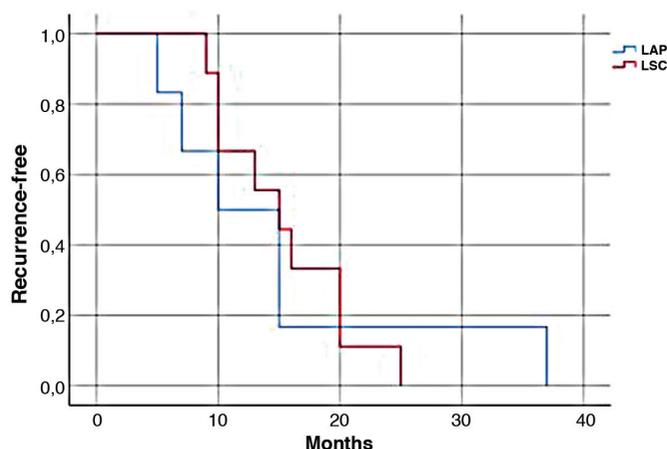


Figure 1. Five-year disease-free survival rates with reference to the surgical procedure (laparotomy vs. laparoscopy) in 151 patients with endometrioid endometrial cancer (p=0.864)

Table 2. Intraoperative parameters and tumor stage

Parameters	LAP (n=71)	LSC (n=80)	Total	p-value
Duration of operation (minute)	173.73±76.52	182.53±90.18	178.38±83.84	0.806 [†]
Lymphadenectomy	46 (65.7%)	42 (53.2%)	88 (59.1%)	0.120 ^{††}
Weight of uterus (g)	142.5	104	-	-
Size of tumor (mm)	34.33±25.67	32.59±18.00	33.58±22.55	0.974 [†]
Invasion depth (mm)	8.56±7.63	5.91±5.46	7.43±6.88	0.099 [†]
Intraoperative blood loss Hb loss; (g/dL)	1.923±1.34	1.317±1.15	1.582±1.27	0.005 [†]
Bladder injury	3 (4.5%)	0 (0.0%)	3 (2.1%)	0.094 ^{†††}
Ureter injury	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Bowel injury	1 (1.5%)	0 (0.0%)	1 (0.7%)	0.459 ^{†††}
FIGO I	52 (73.2%)	64 (80.0%)	116 (76.8%)	0.326 ^{††}
FIGO II	9 (12.9%)	7 (8.8%)	16 (10.7%)	0.416 ^{††}
FIGO III	6 (8.5%)	7 (8.8%)	13 (8.6%)	0.948 ^{††}
Grade 1	43 (61.4%)	50 (62.5%)	93 (62.0%)	0.893 ^{††}
Grade 2	19 (27.1%)	16 (20.0%)	35 (23.3%)	0.302 ^{††}
Grade 3	8 (11.4%)	14 (17.5%)	22 (14.7%)	0.294 ^{††}

(n) indicates the number of patients in each subgroup who reported for evaluation.

LAP: Laparotomy group, LSC: Laparoscopy group, FIGO: International Federation of Gynecology and Obstetrics, [†]Mann-Whitney U test, ^{††}chi-square test, ^{†††}Fisher's exact test

cancer. Our groups were also homogeneous in regard of their ASA scores. In contrast, Schramm et al. (24) reported a poor constitutional status in 55.9% of their 254 patients (ASA score of 3 or 4). A comparison of the present study with previous reports is hindered by these differences (24).

In line with published data, there was a higher median average blood loss in the LAP group than in the LSC group (1.9 vs. 1.3 g/dL). Lu et al. (6) analyzed 272 patients with endometrial cancer prospectively, and noted a statistically significant reduction of blood loss when using the laparoscopic approach compared to the open approach (median blood loss, 86 vs. 419 mL). In a meta-analysis of three randomized controlled trials, comprising 313 patients, laparoscopy was associated with a large and statistically significant reduction in blood loss compared to laparotomy (mean difference, 106.82 mL) (12). However, in our study, blood loss was estimated by the surgeon and determined by the difference in Hb levels before and after surgery.

As expected, the duration of hospital stays was longer in the LAP group than in the LSC group (12.25 days vs. 5.73). However, the mean average duration of hospitalization after laparotomy, as reported in the published literature (3.2 to 8.2 days), is shorter than that registered in the present study. The significantly longer postoperative stay of our patients may be due to the fact that FIGO stage 3 disease was not included in many studies. Moreover, the duration and total flow rate of intraperitoneal drains were significantly greater in women undergoing open surgery, as was the quantity of drainage in 24 hours. However, since the number of resected pelvic lymph nodes did not differ significantly between groups, the higher flow rate in drains may have been due to the traumatic nature of open surgery.

The mean duration of the operation was only five minutes shorter in the LSC than in the LAP group (171 vs. 176 minutes). This is in contrast to Kyrgiou et al. (25), who reported a longer time taken for laparoscopic surgery compared with the open approach (150 vs. 105 minutes). Lu et al. (6) mentioned a shorter median operating time in the LSC group compared with the LAP group (211 minutes vs. 261 minutes, $p < 0.01$). Published data concerning the average duration of laparoscopic procedures for endometrial carcinoma range from 75.8 to 287 minutes, and for open surgery between 79 and 247.8 minutes (20,23,26,27). The large variation in the duration of surgery may be explained by the fact that patients with different FIGO stages, who underwent different operative procedures, were evaluated in these studies.

In general, sufficient and similar numbers of pelvic and para-aortic lymph nodes were removed in both our patient groups. The published literature reports a wide range of resected pelvic lymph nodes by the laparoscopic approach (8.86 to 24.1) or by laparotomy (6.1 to 30.8). Open surgery appears to be more radical in regard of lymphadenectomy (28,29). However, the role and the extent of lymphadenectomy remain a debated issue in the scientific community. The German guidelines recommend the removal of at least 15 pelvic and 10 para-aortic lymph nodes for surgical staging and for selecting the appropriate adjuvant therapy, but provide no data about a potential survival benefit (15). Systematic lymphadenectomy may cause intra- and post-operative complications. According to the GOG 244 trial, systematic lymphadenectomy has a negative impact on quality of life in the majority of patients (30). An update of scientific evidence may well cause clinicians to depart from the policy

Table 3. Postoperative parameters and complication rates

Parameters	LAP (n=71)	LSC (n=80)	Total	p-value
Postoperative days in hospital (d)	12.25±6.40	5.73±3.75	8.72±6.07	<0.001 [†]
Drainage duration (d)	5.91±3.99	3.86±1.80	4.82±3.18	0.003 [†]
Drainage quantity (mL)	1160	370	-	-
Clavien-Dindo 1	48 (68.6%)	69 (87.3%)	117 (78.5%)	0.005 ^{††}
Clavien-Dindo 2	12 (17.1%)	6 (7.6%)	18 (12.1%)	0.074 ^{††}
Clavien-Dindo 3a	0 (0.0%)	4 (5.1%)	4 (2.7%)	0.123 ^{†††}
Clavien-Dindo 3b	7 (10.0%)	0 (0.0%)	7 (4.7%)	0.004 ^{†††}
Clavien-Dindo 4a	3 (4.3%)	0 (0.0%)	3 (2.0%)	0.101 ^{†††}
Clavien-Dindo 4b	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Clavien-Dindo 5	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Clavien-Dindo (mild) Grades 1 and 2	60 (85.7%)	75 (94.9%)	135 (90.6%)	0.054 ^{††}
Clavien-Dindo (severe) Grades 3a-5	10 (14.3%)	4 (5.1%)	14 (9.4%)	0.045 ^{††}

(n) indicates the number of patients in each subgroup who reported for evaluation.

LAP: Laparotomy group, LSC: Laparoscopy group, [†]Mann-Whitney U test, ^{††}chi-square test, ^{†††}Fisher's exact test

of “everything or nothing” to the acceptance of “less is more”, as currently used in breast surgery. This would also signify a departure from purely technical advancements in surgery, towards the achievement of a beneficial oncological outcome for patients.

Despite the larger number of patients with higher FIGO stages of disease, no patient in the LSC group experienced intra-operative injury. In contrast, 4.2% of patients in the open surgery group had bladder injuries and 1.4% had a bowel injury. Complications in the urinary tract in patients with endometrial cancer range from 0.3% to 4.65%, and bowel injuries range between 0.85% and 13.1% (21,31). In a study performed by Cheng et al. (32) comprising 120 patients, obese women with endometrial cancer who underwent laparoscopic surgery had significantly fewer intra-operative and postoperative complication than those who were treated by laparotomy (5.0% vs. 16.7% and 6.7% vs. 20.0%, respectively). Favero et al. (33) noted lower complication rates for laparoscopic surgery compared with open surgery (18% vs. 36%) in patients with type 2 endometrial cancer. We noted similar results for complications based on Clavien-Dindo classification: the LAP group experienced both mild and severe complications significantly more frequently than the LSC group.

The published literature contains meager and very heterogeneous information about postoperative complications according to Clavien-Dindo classification. First-degree complication rates are 25.5-96%, and severe complication rates 5-51.7% (31). However, the above-mentioned data prove that the laparoscopic approach is a safe option for the treatment of endometrial cancer.

We registered no significant difference in disease recurrence rates between LSC (11.3%) and LAP (8.5%). Local recurrences were more common in the LSC group (4 vs. 1), and distant recurrent disease was more common in the LAP group (2 vs. 0). However, reliable statements in this regard are hindered by the fact that most of the recurrences were local as well as distant, and the number of cases was small. In a prospective study with a median follow-up period of 68 months, Lu et al. (6) reported similar results for both groups: recurrence rates were 4.6% for patients treated by the laparoscopic approach versus 5.0% for those treated by open surgery. However, the duration of follow-up varied between 2 and 153 months. Slightly higher recurrence rates were reported by Walker et al. after a three-year follow-up; 11.4% in the LSC group versus 10.2% in the LAP group. We conclude that recurrence rates in patients with endometrial cancer are not related to the open or laparoscopic surgical approach. However, it would be appropriate to analyze locoregional and distant recurrent disease in a large patient population after minimally invasive surgery for endometrial tumors outside the uterus.

A Cochrane meta-analysis of six large studies, assessing 3,993 individuals, yielded no significant difference in overall survival between women who underwent laparoscopy and those who underwent laparotomy (12). Analogous to our data, the 4.5-year overall survival rate was 92.0% in the LSC group and 92.4% in the LAP group. In a randomized clinical trial comprising 122 patients, Tozzi et al. (34) registered overall survival rates of 83% in the LSC group versus 86.5% the LAP group after a median follow-up of 44 months. Our study, one of the few to report overall five-year survival rates, revealed slightly lower overall survival (91.2% vs 97.2%) and median overall survival rates (25 vs. 32 months) for LSC compared to LAP, but the difference was not significant. In fact, the use of minimally invasive surgery in cancer patients is a very controversial issue, especially in cases of advanced endometrial cancer with tumor outside the uterus (14). However, patients older than 60 years of age who underwent laparoscopic staging for uterine cancer had significantly reduced morbidity rates (35). A multivariate analysis of the oncologic outcome in regard of tumor stage, age, and physical status may serve as a basis for devising individual therapy concepts for patients.

Study limitations

The potential limitations of the present analysis include its retrospective design and the absence of randomization. Moreover, the data were derived from a single center. The strengths of the present investigation are the inclusion of homogenous groups, the analysis of postoperative complications according to the Clavien-Dindo classification, and the long duration of follow-up, which permitted analysis of five-year outcomes.

Conclusion

These data highlight the superiority of the laparoscopic approach over open surgery for the treatment of endometrioid endometrial cancer in terms of overall morbidity, intraoperative complications, blood loss, post-surgical recovery, as well as the incidence and severity of postoperative complications in this population. Both approaches permitted a systematic pelvic and para-aortic lymphadenectomy with a sufficient amount of resected lymph nodes. The laparoscopic approach appears to be as safe as the conventional open technique, but provides a better surgical outcome and might therefore be more beneficial for the patient.

Ethics Committee Approval: The study was in compliance with the Helsinki Declaration and was approved by the Ethics Committee of the University of Luebeck (approval number: 18-229A, date: 16.08.2018).

Informed Consent: It was obtained.

Peer-review: Externally peer-reviewed.

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