#### GYNECOLOGIC ONCOLOGY



# Minimally invasive surgery does not impair overall survival in stage IIIC endometrial cancer patients

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#### Abstract

**Purpose** We aimed to evaluate weather survival is impaired in stage IIIC endometrial cancer patients treated with minimally invasive surgery as compared to laparotomy.

**Methods** We analyzed surgical data and oncologic outcome of histologically proven stage IIIC endometrial cancer patients who were treated at our institution via laparotomy or via laparoscopic surgery. All the patients underwent a systematic pelvic and para-aortic lymphadenectomy and a complete tumor resection. Perioperative morbidity and overall survival of the patients subjected to the two surgical approaches were compared.

**Results** Sixty-six patients with stage IIIC endometrial cancer were identified. Of these, 15 patients were operated via laparotomy and 51 via laparoscopy. The two groups were similar with regards to median age at diagnosis, BMI, histotype, number of affected lymph nodes, and median maximal diameter of the affected lymph nodes. Patients undergoing laparoscopic surgery had fewer perioperative complications, a smaller estimated blood loss, and were subjected less frequently to transfusions. Overall survival at 60 months of follow-up did not differ between the two groups. At uni- and multivariate analysis, surgical approach did not affect survival. Only age was a variable associated with overall survival.

**Conclusions** Minimally invasive surgery has better perioperative outcomes and does not impair survival in stage IIIC endometrial cancer patients. Age at diagnosis is the only factor independently affecting survival.

Keywords Endometrial cancer · Laparotomy · Laparoscopy · Lymph node metastases · Overall survival

## Introduction

Endometrial cancer is the most common gynaecological cancer in developed countries. Most patients present with early-stage disease as they usually have symptoms early. The mainstay of treatment is surgery involving total hysterectomy, bilateral salpingo-oophorectomy, and lymphadenectomy. Traditionally surgery is performed via open laparotomy but since the advent of laparoscopy in the 1990s,

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several studies have demonstrated that laparoscopic surgery is a safe and feasible option that is associated with a lower rate of postoperative complications compared to laparotomy in the management of endometrial cancer [1-3].

In 2009, the results of a prospective randomized GOG clinical trial comparing laparotomy to laparoscopic surgery in 2600 patients, the LAP 2 trial, showed that laparoscopy is associated with lesser postoperative complications and shorter hospital stay and defined laparoscopy as the new standard of care for patients with endometrial cancer [2]. A follow-up study on the same group of patients after a median of 60 months showed similar rates of overall survival and a small, statistically non-significant, increase in recurrence rate for patients who were treated with laparoscopy [4]. However, both the LAP 2 trial as well as other studies on this topic mostly involved patients with early-stage disease. To date, there are no studies investigating the safety and feasibility of minimally invasive surgery in endometrial cancer with lymph node involvement but a minimally invasive

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surgery has not been contraindicated (if considered technically feasible by the surgeon) in the belief that the surgical approach would not affect survival.

Recently, the results of the LACC trial, a Phase III randomised controlled trial in patients with early-stage cervical cancer, revealed that laparoscopic surgery is associated with higher recurrence rate and worse overall survival compared to the open approach [5]. These results were unexpected given the large body of retrospective evidence on this topic suggesting that surgical approach does not influence oncologic outcome and raise the question of the appropriateness of minimally invasive surgery in other oncologic settings. Our study aims to ascertain the safety, feasibility, and oncologic outcome of laparoscopic surgery in the management of stage IIIC endometrial cancer with nodal involvement.

### Materials and methods

A retrospective analysis of patients with endometrial cancer and lymph node metastases who were treated surgically at the Department of Obstetrics and Gynecology, University Hospital of Bern and University of Bern was performed. Demographic-, clinical-, and pathologic data were retrieved from an electronic database. Surgical reports and clinical charts were used to integrate missing data. The study was IRB approved (KEK 261/2015).

Patients with histologically confirmed International Federation of Gynecology and Obstetrics (FIGO) stage IIIC endometrial cancer undergoing a surgical treatment consisting in hysterectomy, bilateral salpingo-oophorectomy, and systematic pelvic and para-aortic lymphadenectomy leading to a macroscopically complete resection of the lymph nodes were included in the study. At our institution, a primary laparoscopic approach was introduced in 2008. Before that, a primary laparotomy approach was standard of care for the treatment of endometrial cancer. Based on whether the surgery was performed via laparotomy or laparoscopy, patients were divided into two cohorts.

All patients were staged according to the FIGO stage 2009 [6]. Early postoperative complications were considered if occurring within 30 days from surgery. Overall survival (OS) were calculated from the date of initial surgery to the date of last follow-up or death.

Demographic, clinico-pathologic characteristics, and surgical data of the two cohorts were compared using Fisher's exact test. Duration of follow-up was calculated from the date of surgical treatment to the date of death or last followup. OS was estimated using the Kaplan–Meier method. Factors influencing OS were evaluated based on fitting univariable Cox proportional hazard models.

Multivariate models were fit using stepwise and backward variable selection methods considering all variables with a *p* 

value < 0.10 based at univariate analysis. Associations were summarized using hazard ratios (HRs) and corresponding 95% confidence intervals (Cis). p values < 0.05 were considered statistically significant. Analyses were performed using the GraphPad Prism version 5.00 for Windows (GraphPad Software, San Diego, CA) and Microsoft SPSS version 20.0 for Mac.

### Results

Between October 2001 and November 2015, 66 patients underwent a total hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy for endometrial cancer with metastatic spread to the lymph nodes. The surgery was performed via laparotomy and via laparoscopy in 15 (23.1%) and 51 (66.9%) patients, respectively. No conversions from laparoscopy to laparotomy occurred.

Clinico-pathologic characteristics of the patients, including median age, BMI, histology, and involvement of pelvic and/or para-aortic lymph nodes did not differ between patients treated via laparotomy or laparoscopy (Table 1). Mean age for patients undergoing laparotomy or laparoscopic surgery was 63.2 years and 65 years, respectively. Mean BMI was 26.5 kg/m<sup>2</sup> and 26.6 kg/m<sup>2</sup> for patients undergoing laparotomy and laparoscopy, respectively. Tumors were type I and II in 80% and 20% of the cases for patients undergoing laparotomy, and 86.3% and 13.7% of the cases for patients undergoing laparoscopy, respectively. Metastatic lymph nodes were confined to the pelvis in 66% and 58.8% of the cases for patients undergoing laparotomy and laparoscopy, respectively.

Mean operative time was 264.3 min and 325.8 min for patients undergoing laparotomy and laparoscopy,

Table 1 Clinico-pathologic characteristics of the patients

	LPS (51)	LPT (15)	р
Mean Age in years	65 (±11)	63.2 (±11.2)	0.57
Mean BMI in kg/m <sup>2</sup>	26.6 (±7.4)	26.5 (±7.2)	0.16
Histology			0.55
Endometrioid	44 (86.3%)	12 (80%)	
Others	7 (13.7%)	3 (20%)	
UPSC	1	_	
Clear cell carcinoma	4	2	
Carcinosarcoma	1	1	
Undifferentiated	1		0.59
Stage			0.59
IIIC1	30 (58.9%)	10 (66%)	
IIIC2	21 (41.1%)	5 (33%)	

LPS laparoscopy, LPT laparotomy, UPSC uterine papillary serous carcinoma

respectively (p = 0.07). Mean estimated blood loss was significantly lower for patients undergoing laparoscopy versus laparotomy (890 ml vs. 381.7 ml, p = 0.001). Consequently, patients undergoing laparotomy were transfused significantly more often than patients undergoing laparoscopy (66.7% vs. 19.6%, p = 0.001). The mean number of removed pelvic and para-aortic lymph nodes was similar for patients undergoing laparotomy and laparoscopy, respectively. Similarly, the mean diameter of the greatest lymph node metastases was similar between the two groups: 18.3 mm for patients undergoing laparotomy vs. 17 mm for patients undergoing laparoscopy (p = 0.91). Adjuvant treatment consisting in chemotherapy, radiotherapy or a combination thereof was delivered in over 90% of the cases and was equally distributed between patients undergoing laparotomy and laparoscopic surgery. Surgical data are summarized in Table 2.

Estimated 5-years OS was 80% and 70.6% for patients undergoing open or laparoscopic surgery, respectively (p=0.586; Fig. 1). At multivariable analysis, the surgical approach did not affect OS. At univariate analyses, age and transfusion of packed red blood cells were associated with OS. However, only age maintained prognostic importance at multivariate analysis (Table 3).

Table 2 Surgical data

	LPS (51)	LPT (15)	р
OR time in minutes	325.8 (±112)	264.3 (±125)	0.07
EBL in ml	381.7 (±294)	890 (±962)	0.001
Mean number of removed pelvic lymph nodes	28.7 (±13.6)	27.2 (18.1)	0.71
Mean number of removed para-aortic lymph nodes	17.6 (±9.8)	18.2 (±13.9)	0.88
Perioperative complication (Clavien Dindo 3 and 4)	4 (7.8%)	0	0.56
Mean number of positive pelvic LNs	2.9 (±3.3)	2.5 (±1.4)	0.71
Mean number of positive para-aortic LNs	2.3 (±4.5)	1 (±1.5)	0.39
Number of patients being transfused	10 (19.6%)	10 (66.7%)	0.001
Adjuvant therapy	46 (90.2%)	14 (93.3%)	1

LPS laparoscopy, LPT laparotomy, OR operating room, EBL estimated blood loss, LN lymph nodes

**Fig. 1** Kaplan–Meier curve displaying the overall survival of FIGO IIIC patients undergoing laparoscopic and open surgery. At 60 months of follow-up the overall survival was 80% and 70.6% for patients undergoing open or laparoscopic surgery, respectively (p = 0.586)



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**Table 3** Univariate and multivariate cox regression analysis for overall survival (all patients, n = 66)

	Overall survival				
	Univariate analysis		Multivariate analysis		
	HR (95% CI)	р	HR (95% CI)	р	
Age ( $<65 \text{ vs.} \ge 65$ )	0.24 (0.79–0.731)	0.01	0.2 (0.06–0.63)	0.006	
BMI (<30 vs.≥30)	1.13 (0.45-2.86)	0.78			
LPS vs. LPT	0.71 (0.20-2.45)	0.58			
Transfusions (yes vs. no)	2.69 (1.04–7)	0.04	1.82 (0.61–5.45)	0.28	
Complications (yes vs. no)	2.64 (0.6–11.6)	0.19			
Histotype ( endometriod vs. others)	1.91 (0.62–5.85)	0.25			
Stage (IIIC2 vs. IIIC1)	2.18 (0.82-5.64)	0.1	2.44 (0.81-7.36)	0.11	
Number of positive LNs ( $\geq 4$ vs. < 4)	2.06 (0.79-5.36)	0.13			
Adjuvant therapy (yes vs. no)	0.36 (0.1-1.26)	0.11			

Multivariable models were carried out for variables reporting a p value  $\leq 0.1$  in univariate analysis *LPS* laparoscopy, *LPT* laparotomy

#### Discussion

Our results suggest that laparoscopic surgical staging for stage IIIC endometrial cancer is safe and feasible compared with the same surgery undertaken via laparotomy. The 5-years OS is comparable in patients treated via laparoscopy and laparotomy and correlates well with data reported in the literature, suggesting that a minimally invasive surgery does not impair oncologic outcome provided the resection of the disease is complete. In 2009, the LAP2 study, which involved more than 2600 patients, found that laparoscopy is associated with fewer adverse postoperative outcomes, shorter hospital stays, and longer operating duration [2]. The follow-up study in 2012 found that there was a small increase in cancer recurrence in the laparoscopy group, but the overall survival was similar in both groups [4]. The Laparoscopic Approach to Cancer of the Endometrium (LACE) trial was a multinational, randomized equivalence trial conducted in New Zealand, Australia and Hong Kong, which randomized patients with stage I endometrioid-endometrial cancer into surgery via laparoscopy or laparotomy [7]. They found that the disease-free survival and overall survival were similar in both groups after a follow-up of 4.5 years. However, in both these trials the majority of the enrolled patients had early-stage disease that had not spread to the lymph nodes. Hence, the good overall prognosis of early-stage endometrial cancer patients may have diluted a detrimental effect of a laparoscopic approach. In our series, although relatively small, only patients with documented metastatic disease to the lymph nodes were included. This is the first study assessing the overall survival in a selected cohort of patients with metastatic disease to the lymph nodes.

Concerning the surgical data, although it did not reach statistical significance, the mean operative time was longer in the group of patients treated via laparoscopy as compared to those treated via laparotomy (325.8 vs 264.3 min). This reflects the complexity of the surgery. Already in circumstances where the lymph nodes are not involved, the pelvic and para-aortic lymphadenectomy may require a longer operative time. This complexity is further increased in case of lymph nodal involvement, as the involved tissues may be more adherent and relatively fixed.

On the contrary, the estimated blood loss was significantly higher for patients treated via laparotomy as compared to those treated laparoscopically. This resulted in a higher number of patients being transfused in the laparotomy group. These latter data are congruent with those reported in a systematic review and a meta-analysis on randomized controlled trials that showed that laparoscopy is associated with less bleeding and transfusions [8, 9]. Furthermore, laparoscopy proved to have a faster recovery, less postoperative pain, and a shorter hospital stay [8, 9]. Other series have proven the minimally invasive approach to be beneficial over laparotomy also in terms of perioperative complications [10]. Each 10% increase in minimally invasive surgery would save \$2.8 million and 41 postoperative complications. If used exclusively, minimally invasive surgery would save 6434 hospital days and 416 complications. A retrospective study of 383 patients with high grade endometrial cancer found that patients treated via a minimally invasive approach experienced fewer perioperative complications and similar recurrence and survival outcomes when compared to their laparotomy-treated counterparts [11]. They found that the mean operating time was longer and the mean lymph node count (39 vs. 34) was higher in the minimally invasive group. Favero et al. studied 89 patients with serous or clear-cell endometrial cancer who were treated with laparoscopy or laparotomy [12]. They also found similar survival outcomes in both groups. The mean number of lymph nodes removed was higher in the laparoscopy group. Monterossi et al. conducted a retrospective trial, which found that women with type II endometrial cancers submitted to laparoscopic surgery, experienced fewer perioperative complications than those who underwent laparotomy, with similar patterns of recurrence and survival outcomes [13]. The pattern of recurrence and rate of local recurrence were also similar in both groups, thereby confirming that surgical route does not affect the chance of recurrence.

A critical aspect of the treatment of stage IIIC endometrial cancer patients is the removal of the entire disease. In our series, the mean number of lymph nodes removed were similar for both surgical techniques even after breaking down to pelvic and para-aortic lymph nodes. The type of nodal metastases was also similar in both groups. Obermair, Koskas, and Gao reported fewer lymph nodes removed in the laparoscopy group compared to the laparotomy group [14–16]. Other series have demonstrated that the two techniques are comparable in terms of retrieved lymph nodes [1-3, 8, 9]. In our series, the median maximal diameter of the lymph node metastases was 18.3 mm and 17 mm for the patients being treated via laparotomy and via laparoscopy. It seems therefore that the laparoscopic completion of a systematic pelvic and para-aortic lymphadenectomy is technically feasible also when the lymph nodes are macroscopically involved. Whenever the completeness of the resection of the involved lymph nodes is put at hazard by the minimally invasive approach, a conversion to a laparotomy should be performed to ensure a complete resection of the disease as this is a critical prognostic factor in the treatment of endometrial cancer patients [17, 18]. This may occur if the metastatic disease becomes too bulky although it is difficult to define a cut off diameter.

With multivariate regression analysis, we found that the only factor, which affects survival independently, is age. Age less than 65 years old significantly improves survival with a hazard ratio of 0.24 (p = 0.01). Secondary analyses of a randomized-controlled trial investigating the effect of pelvic lymphadenectomy on early-stage endometrial cancer found that age more than 65 years old was a poor prognostic factor [19]. The 5-years overall survival of patients more than 65 years old was worse by about 10% compared to younger patients (92.1% vs. 78.4%, p < 0.0001). This result was the same regardless of nodal involvement. The PORTEC trial and Gynecologic Oncology Group study (GOG-99), which investigated adjuvant radiotherapy in endometrial cancer, also found that age was a poor prognostic factor [20, 21]. Some may argue that patients who are older have an increased incidence of type II endometrial cancer with poorer prognosis. However, in our study, more than 80% of patients have endometrioid adenocarcinoma of the endometrium and thus limiting this bias.

The results of our study may open new possibilities in the treatment of endometrial cancer patients with lymph nodal

metastases. The S3 guidelines for the treatment of endometrial cancer recommend a minimally invasive approach in patients with presumed early-stage disease [22]. However, if our results are confirmed by further studies, the indication to a minimally invasive approach might be broadened also to more advanced stages, provided that the entire disease is removed.

We recognize there are several limitations to our study, including the retrospective nature and the relatively low number of patients in our cohort. However, this study is the first study that is addressing the oncologic outcome of laparoscopic surgery in advanced stage endometrial cancer. We also have a high level of laparoscopic expertise in our centre as accredited laparoscopic surgeons perform these surgeries. As a small group of surgeons performed the surgeries in a single institution, the homogeneity of treatment is assured. We conclude that laparoscopic surgery is safe and feasible for patients with stage IIIC endometrial cancer. Further evidence needs to confirm our results given the retrospective nature of or study.

Author contribution AP: concept, manuscript writing and editing, and supervision. MDM: concept, manuscript editing, and supervision. MLG: statistical analysis, manuscript writing and editing, and supervision. JW: manuscript writing and editing, supervision. APR: Data acquisition, manuscript writing and editing, and supervision. AG: data acquisition.

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#### **Compliance with ethical standards**

**Conflict of interest** Andrea Papadia has no conflict of interest. Alicia Garbade has no conflict of interest. Maria Luisa Gasparri has no conflict of interest. Junjie Wang has no conflict of interest. Anda Petronela Radan has no conflict of interest. Michael D Mueller has no conflict of interest.

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