RESEARCH ARTICLE

Comparison of Perioperative and Oncologic Outcomes with Laparotomy, and Laparoscopic or Robotic Surgery for Women with Endometrial Cancer

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Abstract

Purpose: To compare perioperative outcomes and oncologic outcomes in endometrial cancer patients treated with laparotomy, and laparoscopic or robotic surgery. Materials and Methods: Endometrial cancer patients who underwent primary surgery from January 2011 to December 2014 were retrospectively reviewed. Perioperative outcomes, including estimated blood loss (EBL), operation time, number of lymph nodes retrieved, and intra and postoperative complications, were reviewed. Recovery time, disease free survival (DFS) and overall survival (OS) were compared. Results: Of the total of 218 patients, 143 underwent laparotomy, 47 laparoscopy, and 28 robotic surgery. The laparotomy group had the highest EBL (300, 200, 200 ml, $p<0.05$) while the robotic group had the longest operative time (302 min) as compared with laparoscopy (180 min) and laparotomy (125 min) ($p<0.05$). Intra and postoperative complications were not different with any of the surgical approaches. No significant difference in number of lymph nodes retrieved was identified. The longest hospital stay was reported in the laparotomy group (four days) but there was no difference between the laparoscopy (three days) and robotic (three days) groups. Recovery was significantly faster in robotic group than laparotomy group (14 and 28 days, $p=0.003$). No significant difference in DFS and OS at 21 months of median follow up time was observed among the three groups. Conclusions: Minimally invasive surgery has more favorable outcomes, including lower blood loss, shorter hospital stay, and faster recovery time than laparotomy. It also has equivalent perioperative complications and short term oncologic outcomes. MIS is feasible as an alternative option to surgery of endometrial cancer

Keywords: Endometrial cancer - laparoscopy - laparotomy, minimally invasive surgery - robotic surgery - survival

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Introduction

Endometrial cancer is the most common gynecologic malignancy in Western countries. (Siegel et al., 2014) However, it is the third most common cancer in Thailand. (GLOBOCAN, 2012) Hysterectomy with surgical staging is the mainstay treatment for endometrial cancer, traditionally performed through laparotomy. Minimally invasive surgeries (MIS) including laparoscopic and robotic surgery have been widely used due to their better surgical outcomes, shorter hospitalization, and faster recovery than conventional laparotomy. (Gala et al., 2014) Since the approval in 2005 for using robotic surgery, its use has grown exponentially. It has a shorter learning curve than conventional laparoscopy and experience in laparoscopy is not prerequisite. (Yim and Kim, 2012) Our previous study reported that robotic surgery for gynecologic cancers is feasible, safe, with fast recovery, and high patient satisfaction. (Manchana et al., 2014) In Thailand, comparative studies among laparotomy, laparoscopy, and robotic surgery are limited. Therefore, this study aims to compare the perioperative and oncologic outcomes of these three surgical approaches in endometrial cancer patients.

Materials and Methods

A retrospective review of endometrial cancer patients who underwent primary surgery at King Chulalongkorn Memorial Hospital from January 2011 to December 2014 was conducted. Surgical techniques included conventional laparotomy, laparoscopic, and robotic surgery. Patients with histological confirmation of uterine sarcoma, synchronous endometrial and ovarian cancer, and those who had primary radiotherapy were excluded. Surgical techniques were discussed and chosen by the preference of both surgeons and patients.

Patient characteristics such as age, parity, menopausal

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status, body mass index (BMI) and pathological data such as surgical stage, histologic type, tumor grade, myometrial invasion, lymph node involvement, number of lymph nodes retrieved, and adjuvant treatment were obtained. Surgical stage was classified according to the FIGO 2009 staging. (Pecorelli, 2009) Perioperative data including estimated blood loss (EBL), operative time, conversion rate, intra and postoperative complications were recorded. Febrile morbidity was defined as body temperature more than 38 °C in two consecutive measurements at least six hours apart, excluding the first 24 hours. Postoperative pain was evaluated every six hours on the first to third postoperative day (POD) by visual analogue scale (VAS): 0 - 10 scores (0 - no pain; 10 - worst pain). The worst score in each day was used for analysis. Patients were discharged if they could ambulate and have no significant complications. Length of hospital stay and recovery time were also recorded.

All patients were scheduled to follow up every three months for the first two years, every six months for the next three years and yearly thereafter. Disease free survival (DFS) was defined as time from surgery to date of recurrence or last follow up in those without recurrence of disease. Overall survival (OS) was defined as time from surgery to death or last follow up.

Categorical data were presented as percentage and

Table 1. Demographic data and Pathological Findings

	Conventional laparotomy (N=143)	Laparoscopic surgery (N=47)	Robotic surgery (N=28)	P value
Age, years	59 (53-65)	54 (49-62)	55.5 (48.2-61.5)	0.01*1,2
Parity	2 (0-3)	0 (0-2)	1 (0-2)	0.06
Menopause, n (%)	109 (76.5)	30 (63.8)	16 (57.1)	0.06
BMI, kg/m^2	25.4 (22.5-30.2)	24.5 (21.8-28.3)	26.8 (22.7-35.6)	0.17
Obesity (BMI >30kg/m^2), n (%)	40 (26.8)	8 (16.7)	10 (35.7)	0.16
Medical comorbidity, n (%)	98 (68.5)	24 (51.1)	16 (57.1)	0.07
Previous pelvic surgery, n (%)	35 (24.5)	3 (6.4)	8 (28.6)	0.02*1,3
Histology, n (%)				
Endometrioid	131 (91.6)	47 (100)	28 (100)	0.05
Clear cell	6 (4.2)	0 (0)	0 (0)	0.2
Serous	3 (2.1)	0 (0)	0 (0)	0.45
Mixed cell	3 (2.1)	0 (0)	0 (0)	0.45
Tumor grade, n (%)				
1	76 (53.1)	35 (74.5)	20 (71.4)	0.01*1
2	26 (18.2)	7 (14.9)	3 (10.7)	0.53
3	41 (28.7)	5 (10.6)	5 (17.9)	0.04 *1
Myometrial invasion, n (%)				
No	21 (14.7)	8 (17)	5 (17.9)	0.87
Less than 50%	53 (37.1)	28 (59.6)	14 (50.0)	0.02*1
More than 50%	69 (48.3)	11 (23.4)	9 (32.1)	0.01*1
FIGO stage, n (%)				
I	94 (65.7)	42 (89.4)	20 (71.4)	0.01*1
II	12 (8.4)	1 (2.1)	6 (21.4)	0.02*3
III	27 (18.9)	4 (8.5)	2 (7.1)	0.1
IV	10 (7)	0 (0)	0 (0)	0.06
FIGO stage, n (%)				
Early	106 (74.1)	43 (91.5)	26(92.9)	0.01*1
Advance	37 (25.9)	4 (8.5)	2 (7.1)	0.01*2
Complete surgical staging, n (%)	71 (48.3)	17 (36.2)	19 (67.8)	0.03*3
No lymphadenectomy, n (%)	21 (14.7)	2 (4.2)	0 (0)	0.02*1,2
Pelvic node metastasis, n (%)	15 (12.3) (N=122)	3 (6.7) (N=45)	1 (3.6) (N=28)	0.27
Paraaortic node metastasis, n (%)	3 (4.1) (N=71)	0 (0) (N=17)	0 (0) (N=19)	0.47
Pelvic nodes retrieved (IQR)	14 (10-18)	16.5 (12-23.7)	15 (10-20.7)	0.18
Paraaortic nodes retrieved	3 (2-5)	3 (2-6)	6 (2-8)	0.06
Adjuvant treatment, n (%)				
No treatment	58 (40.6)	34 (72.3)	16 (57.1)	0.001*1
Radiation only	50 (35.0)	10 (21.3)	9 (32.1)	0.22
Chemotherapy + Radiation	27 (18.9)	3 (6.4)	3 (10.7)	0.09
Chemotherapy only	7 (4.9)	0 (0)	0 (0)	0.15
Refused	1 (0.6)	0 (0)	0 (0)	0.77

All continuous data were shown in median (interquartile range); BMI: Body mass index; Complete surgical staging: hysterectomy with bilateral salpingooophorectomy with pelvic and paroaortic lymphadenectomy; *1- Statistically significant difference between conventional laparotomy and laparoscopic surgery group; *2- Statistically significant difference between conventional laparotomy and robotic surgery group
*3- Statistically significant difference between laparoscopic and robotic surgery groups

compared between groups with Chi-square or Fisher Exact test. Continuous data were tested for normality by Kolmogorov-Smirmov. Nonparametric data were shown as median and interquartile range (IQR). Comparisons of these variables were analyzed by Kruskal-Wallis. DFS and OS were analyzed by the Kaplan-Meier and log rank test was used to assess the statistical significance among the three surgical approaches. A p value of less than 0.05 was considered as statistical significance.

Results

Among 218 endometrial cancer patients, 143 patients (65.6%) were in the laparotomy, 47 patients (21.6%) in the laparoscopy, and 28 patients (12.8%) in the robotic group. Demographic data and pathological findings are shown in Table1. The median age of all patients was 57 years (IQR, 51-64 years); patients in the laparotomy group were significantly older than the other groups. More patients in the laparotomy group had advanced stage, tumor grade 3 and deep myometrial invasion ($p<0.05$). These findings were significantly different only between the laparotomy and laparoscopy group. Most of the patients underwent hysterectomy with pelvic lymphadenectomy, occurring in 85.3%, 95.7% and 100% in the laparotomy, laparoscopy, and robotic group, respectively ($p=0.02$). Paraaortic lymphadenectomy was optional. The robotic group had the highest rate of complete surgical staging including pelvic and paraaortic lymphadenectomy (67.8%), while the laparoscopy group had the lowest rate (36.2%) ($p=0.03$). No significant difference in the number of pelvic nodes retrieved was identified. However, more paraaortic nodes retrieved were found in the robotic group and the difference trended to near statistical significance ($p=0.06$).

Perioperative outcomes are shown in Table 2. The laparotomy group had the highest EBL but shortest operative time when compared with the laparoscopy and robotic group ($p<0.05$). The robotic group had the longest operative time followed by the laparoscopy and the laparotomy group, respectively ($p<0.05$). Overall intraoperative and postoperative complications were not significantly different for any surgical approaches. However, febrile morbidity was more frequent in the laparotomy group ($p=0.02$). Furthermore, the laparotomy group required more blood transfusion, although there was no significant difference. Two patients in the laparoscopic group (4.2%), one had inferior vena cava injury and the other had ureteric injury that required conversion to laparotomy to control bleeding and undergo ureteric repair. No patient in the robotic group required conversion. Perioperative death occurred in one patient in the laparotomy group due to pulmonary embolism.

In subgroup analysis of 57 obese patients (BMI > 30kg/m2) compared to 161 non-obese patients, showed significantly higher postoperative complications (28.1% vs. 9.3%, $p=0.001$).Wound complications were particularly common (19.3% vs. 3.1%, $p<0.001$), especially wound infection (14% vs. 3.7%, $p=0.01$) and wound dehiscence (8.8% vs. 0.6%, $p=0.005$). Furthermore, all patients who developed thromboembolism occurred in obese patients who underwent laparotomy (5.3% vs. 0%, $p=0.02$). Perioperative outcomes were compared among three different groups as shown in Table 3. Intraoperative complications especially visceral organ injuries were

Table 2. Perioperative Outcomes

	Conventional laparotomy (N=143)	Laparoscopic surgery (N=47)	Robotic surgery (N=28)	P value
Estimated blood loss, ml	300 (200-500)	200 (100-350)	200 (100-200)	<0.01*1,2
Operative time, minutes	125 (100-150)	180 (130-210)	302 (277.5-360)	<0.01*1-3
Intraoperative complication, n (%)	18 (12.6)	5 (10.6)	2 (7.1)	0.7
Visceral organ injuries, n (%)	9 (6.3)	4 (8.5)	2 (7.1)	0.87
Blood transfusion, n (%)	12 (8.4)	1 (2.1)	0 (0)	0.11
Postoperative complication, n (%)	19 (13.3)	7 (14.9)	5 (17.8)	0.81
Febrile morbidity, n (%)	24 (16.8)	2 (4.2)	1 (3.6)	0.02*1
Wound complication, n (%)	12 (8.4)	2 (4.2)	2 (7.1)	0.64
Wound infection, n (%)	10 (7)	2 (4.2)	2 (7.1)	0.79
Wound dehiscence, n (%)	6 (4.2)	0 (0)	0 (0)	0.2
Vaginal cuff disruption, n (%)	0 (0)	1 (2.1)	0 (0)	0.16
Thromboembolism, n (%)	3 (2.1)	0 (0)	0 (0)	0.45
Intraabdominal bleeding /hematoma, n (%)	2 (1.4)	0 (0)	0 (0)	0.59
Pain scores on the first postoperative day	3 (2-5)	3 (1-5)	3 (2-5)	0.78
Pain scores on the second postoperative day	2 (1-4)	1 (0-3)	2.5 (0.25-3.75)	0.02*1
Pain scores on the third postoperative day	2 (0-3) (N=132)	1 (0-2) (N=36)	0 (0-3) (N=23)	0.07
Hospital stay ,days	4 (3-6)	3 (3-4)	3 (2-9)	<0.01*1,2
Recovery time ,days	28 (14-30)	17.5 (7-30)	14 (7-21)	0.003*2

All continuous data were shown in median (interquartile range); VAS: Visual analog scale; *1- Statistically significant difference between conventional laparotomy and laparoscopic surgery group; *2- Statistically significant difference between conventional laparotomy and robotic surgery group; *3- Statistically significant difference between laparoscopic and robotic surgery groups

Table 3. Perioperative outcomes in obese patients (BMI>30kg/m²)

	Conventional laparotomy (N=40)	Laparoscopic surgery (N=7)	Robotic surgery (N=10)	P value
Estimated blood loss ,ml	450 (300-775)	200 (100-500)	200 (100-325)	0.01*2
Operative time ,minutes	127.5 (101-150)	240 (210-330)	350 (294-395)	<0.01*1-3
Intraoperative complication, n (%)	3 (7.5)	2 (28.6)	0 (0)	0.11
Visceral organ injuries, n (%)	1 (2.5)	2(28.6)	0 (0)	0.01*1
Blood transfusion, n(%)	2 (5.0)	0 (0)	0 (0)	0.64
Postoperative complication, n (%)	12 (30)	2 (28.6)	2 (20)	0.82
Febrile morbidity, n (%)	9 (22.2)	0 (0)	0 (0)	0.1
Wound complication, n (%)	9 (22.5)	1 (14.3)	1 (10)	0.63
Wound infection, n (%)	6 (15)	1 (14.3)	1 (10)	0.92
Wound dehiscence, n (%)	5 (12.5)	0 (0)	0 (0)	0.31
Thromboembolism, n (%)	3 (7.5)	0 (0)	0 (0)	0.51
Intraabdominal bleeding/ hematoma, n (%)	1 (2.5)	0 (0)	0 (0)	0.8

All continuous data were shown in median (interquartile range); *1- Statistically significant difference between conventional laparotomy and laparoscopic surgery group; *2- Statistically significant difference between conventional laparotomy and robotic surgery group; *3- Statistically significant difference between laparoscopic and robotic surgery groups

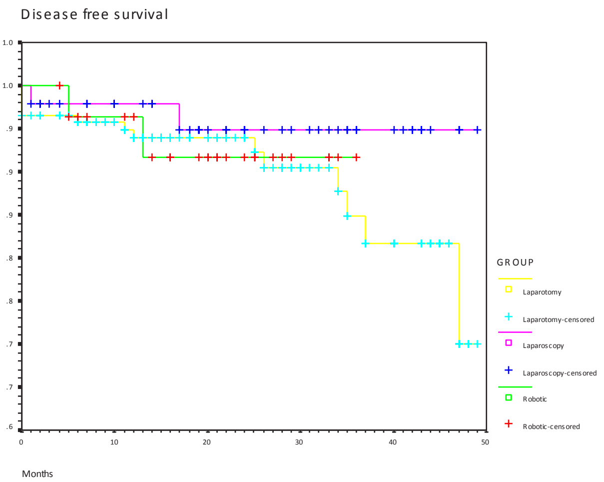

Figure 1. Disease free Survival

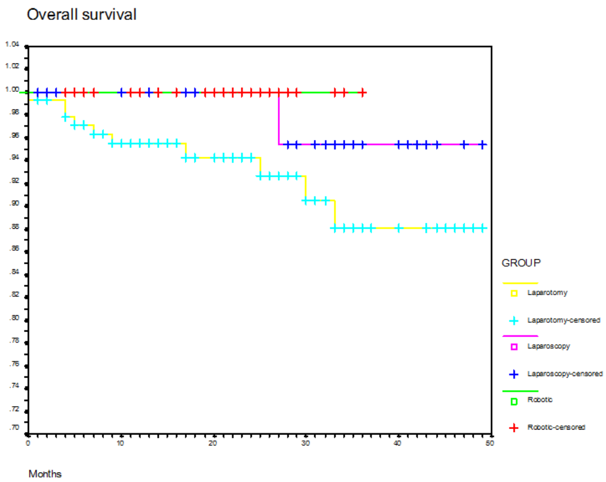

Figure 2. Overall Survival

significantly more frequent in the laparoscopic group. Although overall postoperative complications were not significantly different, specific complications such as febrile morbidity, wound dehiscence, thromboembolism, and intraabdominal bleeding occurred only in the laparotomy group.

A significantly longest hospital stay was reported in the laparotomy group but there was no difference between the laparoscopy and robotic group. Median recovery time was significantly shortest in the robotic group (14 days) but longest in the laparotomy group (28 days). Median follow up time for the laparotomy group was 20 months (IQR, 11-33 months), 24 months (IQR, 14-36 months) for the laparoscopy group, and 21 months (IQR, 14.5-27.7months) for the robotic group. Fifteen patients (10.5%) in the laparotomy group, two (4.2%) in the laparoscopic group, and two (7.1%) in the robotic group had recurrent diseases (P=0.52). Port site metastasis occurred in two patients in the robotic group; both of them were in stage 3. Six patients in the laparotomy group died after recurrence (40%). Treatment related death occurred in four patients; one developed pulmonary embolism and death on the third postoperative day, onehad septicemia after the fifth cycle of chemotherapy, one developed bowel obstruction and pulmonary embolism at the fourth month postoperatively, and another had radiation induced bowel perforation at the 30th monthpostoperatively). One patient died from a non-cancer cause (pneumonia). Only one patient in the laparoscopy group (50%) and none in the robotic group died after occurrence of recurrent disease. No significant difference in DFS and OS at 21 months of median follow up time (IQR, 11-33 months) was observed among these three surgical approaches (Figure 1, 2).

Discussion

Worldwide, there has been an increase in the use of MIS in gynecologic cancers, especially endometrial cancer. From one survey MIS increased significantly from 16% in 2006 to 48% in 2010. (Scalici et al., 2015) About 34% (75/218 patients) of our endometrial cancer patients during 2011 to 2014 underwent surgical staging with MIS approaches. Many studies show a preference to MIS over conventional laparotomy. They showed positive outcomes such as less blood loss, reduced operative morbidity, shorter hospital stays, earlier return to work, and better quality of life. (Kornblith et al., 2009 ; Walker et al., 2009; Galaal et al., 2012 ; Wang et al 2013) These findings were similar to our study where MIS, either laparoscopic or robotic surgery, had significantly less blood loss and shorter hospital stays. Although, MIS had a faster recovery time in our study, the statistical significance was observed only between the robotic and laparotomy group. One major disadvantage of MIS was longer operative time. The operative time for robotic surgery was similar to laparoscopic surgery but was longer than laparotomy. (Ran et al., 2014) In our study, the robotic group had longer operative time than the laparoscopic group and, in fact, had the longest operative time. The da Vinci Surgical System® (Intuitive Surgical Inc, Sunnyvale, CA) has been available in our hospital since 2011. Therefore, the 28 patients in the robotic group could be considered to be part of our initial learning curve. Furthermore, significantly more patients in the robotic group had complete surgical staging, including pelvic and paraaortic lymphadenectomy. These factors may contribute to the longer operative time, as we mentioned in our previous study. (Manchana et al., 2014) A larger number of patients are needed to achieve proficiency and thereby reduce the operative time.

A recent meta-analysis showed significantly reduced blood loss, fewer conversions, and fewer complications with robotic surgery than with laparoscopy and laparotomy. (Ran et al., 2014) This may be due to the advantages of robotic surgery over traditional laparoscopy, such as better visualization, more ergonomic control, and wristed instruments improving surgical precision. Our study showed that the laparotomy group had significantly more EBL and non-statistically more blood transfusions. However, no significant difference in these outcomes was found between the laparoscopy and robotic group. Ran's study showed 8.2% and 4.3% conversion rate in laparoscopy and robotic group, respectively ($p<0.05$). Although a higher conversion rate (4.2%) was found in the laparoscopy group and none in the robotic group, the difference did not reach statistical significance.

Significant increases in postoperative complications especially wound complications, were reported in association with laparotomy. (Gaia et al., 2010; Scalici et al., 2015) Although, we could not find a significant difference in overall postoperative complications, febrile morbidity was significantly higher in the laparotomy group than in the laparoscopy group. Furthermore, a higher rate of wound complication particularly wound dehiscence was prevalent in the laparotomy group especially in the subgroup of obese patients.

Our study reported no statistical significance in lymph node retrieval among these three groups. However, the trend in the number of paraaortic nodes retrieved favored the robotic group, although it was not significant. The advantages of robotic surgery may promote resection of paraaortic lymph nodes more easily and with more precision. However, a larger number of patients may have confirmed the significance. MIS techniques, either laparoscopy or robotic surgery, should be considered to be at least as adequate as laparotomy for surgical staging of endometrial cancer from the perspective of number of lymph nodes retrieved and perioperative complications.

Obesity is associated with an increased risk of developing several malignancies, including endometrial cancer. Unsurprisingly, surgical morbidities should be more prevalent than in non-obese patients. Significantly higher postoperative complications in obese patients, especially wound complications, were reported in our study especially in the laparotomy group. Minimizing complications in this population are being interested. The potential for decreased postoperative complications, especially wound complications and length of hospital stay, may offer many benefits to the obese population. (Gehrig et al., 2008) MIS had significantly reduced blood loss, reduced need for blood transfusion, fewer risks of complications, less postoperative pain, shorter hospital stays, and faster return to work than laparotomy. (Seamon et al., 2009; Martineket al., 2010) Therefore, the MIS approach should be considered in the obese subgroup. One major drawback of laparoscopy is the increased risk of conversion with increasing BMI. (Walker et al., 2009) Therefore, robotic surgery is more promising; it is associated with shorter operative time, less blood loss, increased lymph node retrieval and shorter hospital stays when compared with laparoscopy. (Gehrig et al., 2008) Our study also reported increased visceral organ injuries in the laparoscopy group when compared to the robotic group. From these results, robotic surgery may be an alternative to laparoscopy in particular for obese or morbidly obese patients.

Long term oncologic outcomes of these three approaches are limited. The Gynecologic Oncology Group (GOG) conducted a randomized controlled trial study (LAP2) comparing laparoscopic surgery and laparotomy. No difference in estimated 3-year DFS (88.6% *vs* 89.8%) was reported and the estimated 5-year OS was equal in both groups (89.8%). (Walker et al., 2012) Despite there being no randomized trials between laparoscopic and robotic surgery, no significant difference in survival has been reported from retrospective studies. (Cardenas-Goicoechea et al., 2014 ; Chiou et al., 2015) The estimated 3-year DFS was similar, 83.3% in the robotic group and 88.4% in the laparoscopy group. The 3-year OS was 93.3% in the robotic group and 93.6% in the laparoscopy group. (Cardenas-Goicoechea et al., 2014) These findings were comparable to our study. No significant difference in OS and DFS at short term follow up (21 months) was observed among these three surgical approaches. Laparoscopic or robotic surgery should have equivalent oncologic outcomes when compared to laparotomy. However, longer follow up and randomized trials are needed to confirm these findings.

This is the first and largest study in Thailand to compare surgical and oncologic outcomes between MIS and conventional laparotomy in endometrial cancer patients. A limitation of this study is its retrospective design, which might have caused selection bias. Previous systematic review included eight retrospective comparative studies that reported patients who underwent laparotomy were the oldest, whereas those who underwent robotic surgery or laparoscopy had similar ages. (Gaia et al., 2010) This finding was similar to our study where the laparotomy group was older than the laparoscopy and robotic group. More patients with previous pelvic surgery underwent laparotomy and robotic surgery than laparoscopy. Unfavorable pathologic findings were found more frequently in the laparotomy group. Patients who were in a clinically advanced stage typically performed by laparotomy since MIS may increase the risk of port site metastasis. As a result, more patients in advanced stage with poor histologic grade and deep myometrial invasion underwent laparotomy in our study. Although, baseline characteristics were not similar, our study reported similar outcomes as did previous studies. (Gaia et al., 2010; Ran et al., 2014) MIS has been proven to have more favorable perioperative outcomes including less blood loss, shorter hospital stays, and faster recovery time than laparotomy, although operative time is longer. It also has equivalent short term oncologic outcomes when compared to laparotomy.

Minimally invasive surgery (MIS) results in better outcomes in many aspects such as less blood loss, shorter hospital stay and recovery time when compared to conventional laparotomy. These outcomes were not different between the laparoscopy and the robotic group. However, robotic surgery seemed to have better surgical outcomes than laparoscopy in obese patients. Perioperative complications and oncologic outcomes were equivalent between MIS and laparotomy. Therefore, MIS is feasible and might be an alternative option to laparotomy for surgical staging in endometrial cancer. In particular, it may have some added value in morbidly obese patients.

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