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Comparative Survival Outcome of Robot-Assisted Staging Surgery Using Three Robotic Arms versus Open Surgery for Endometrial Cancer

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Purpose: There is lack of data on direct comparison of survival outcomes between open surgery and robot-assisted staging surgery (RSS) using three robotic arms for endometrial cancer. The purpose of this study was to compare the overall survival (OS) and disease-free survival (DFS) between open surgery and RSS using three robotic arms for endometrial cancer.
Materials and Methods: Consecutive women with endometrial cancer who underwent surgery between May 2006 and May 2018 were identified. Robotic procedures were performed using the da Vinci robotic system, and the robotic approach consisted of three robotic arms including a camera arm. Propensity score matching, as well as univariate and multivariate Cox regression of OS and DFS were performed according to clinicopathologic data and surgical method.
Results: The study cohort included 423 unselected patients with endometrial cancer, of whom 218 underwent open surgery and 205 underwent RSS using three robotic arms. Propensity score-matched cohorts of 146 women in each surgical group showed no significant differences in survival: 5-year OS of 91% vs. 92% and DFS of 86% vs. 89% in the open and robotic cohorts, respectively (hazard ratio, 1.02; 95% confidence interval, 0.82–1.67). In the univariate analysis with OS as the endpoint, surgical method, age, stage, type II histology, grade, and lymph node metastasis were independently associated with survival. Surgical stage, grade, and type II histology were found to be significant independent predictors for OS in the multivariate analysis.
Conclusion: RSS using three robotic arms and laparotomy for endometrial carcinoma had comparable survival outcomes.

Key Words: Endometrial cancer, robot-assisted surgery, survival

INTRODUCTION

Endometrial cancer is the most common malignancy of the female reproductive tract in developed countries.[1] Most patients with endometrial cancer present at an early stage; thus, surgery is often the first major step in the management of this disease. Conventionally, surgery is performed via a midline laparotomy, which is known to be associated with substantial perioperative morbidity.[2,3]

Minimally invasive surgery (MIS) provides equivalent oncologic outcomes when used for endometrial cancer treatment with reduced surgical and postoperative morbidity.[4-6] However, the well-known steep learning curve of a laparoscopic procedure restricts its widespread application in the surgical treatment for endometrial cancer. The introduction of robot-assisted staging surgery (RSS) with a relatively shallow learning curve has facilitated more gynecologic oncologists to employ MIS over open surgery when treating endometrial cancer.[7,8]

Previous research comparing open surgery with laparosco-

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py[5,6,9] and laparoscopy with robot-assisted surgery exists,[10,11] along with a meta-analysis comparing all three approaches.[12,13] However, there is a scarcity of data with respect to direct comparison of survival outcomes between open surgery and RSS using three robotic arms for endometrial cancer.[7,14-16] However, only few published studies have focused on the placement and the number of robotic arms used in the procedure.[17-19]

Therefore, this research aimed to assess the survival outcome of RSS using three robotic arms, and to compare it with that of staging laparotomy after propensity score matching among patients from a single tertiary institution. We hypothesized that RSS with three robotic arms would yield equivalent oncologic outcomes when compared to open surgery for endometrial cancer.

MATERIALS AND METHODS

Patients

All consecutive patients who underwent open staging laparotomy or da Vinci RSS using three robotic arms for endometrial cancer between May 2006 and May 2018 at a single institution were reviewed. Our research was performed in accordance with the ethical tenets of the Declaration of Helsinki, and was approved by the Institutional Review Board (IRB) of Yonsei University College of Medicine (ethic code: 4-2019-0817).

Surgery and outcomes

The mode of surgery was selected mainly based on the surgeon's discretion. Demographic and clinical characteristics (age at diagnosis and body mass index), pathological characteristics [histologic type, grade, and the International Federation of Gynecology and Obstetrics (FIGO) stage], perioperative characteristics (surgical approach, type of procedures performed, number of harvested lymph nodes, and conversion to laparotomy), adjuvant therapy (radiation, chemotherapy, or both), and survival outcomes (recurrence and vital status) were collected from the electronic medical records. Disease-free survival (DFS) was defined as the time interval between the date of initial diagnosis and that of disease progression based on the Response Evaluation Criteria in Solid Tumours (version 152 1.1).[20] We calculated the overall survival (OS) as the time interval between the date of initial diagnosis and that of cancer-related death or the end of the study.

All patients underwent complete surgical staging for endometrial cancer, including hysterectomy, salpingo-oophorectomy, lymph node dissection (pelvic with/without paraaortic nodes), omentectomy, and peritoneal biopsies when required. Robot-assisted surgeries were performed using the da Vinci robotic surgical system (Intuitive Surgical Inc., Sunnyvale, CA, USA) with the Maryland Bipolar and Permanent Cautery Spatula or needle holder on each robotic arm, as described previously.[17,18] Port placement of the RSS using three robotic arms is presented in Fig. 1.

Statistical analyses

Categorical variables were evaluated using Pearson's chi-squared test or Fisher's exact test depending on the category size, whereas Student's t-test was used for comparing continuous variables. The Kaplan-Meier method was used to estimate the survival function. Using the proportional hazards model, we estimated the hazard ratios for each of the following vari-

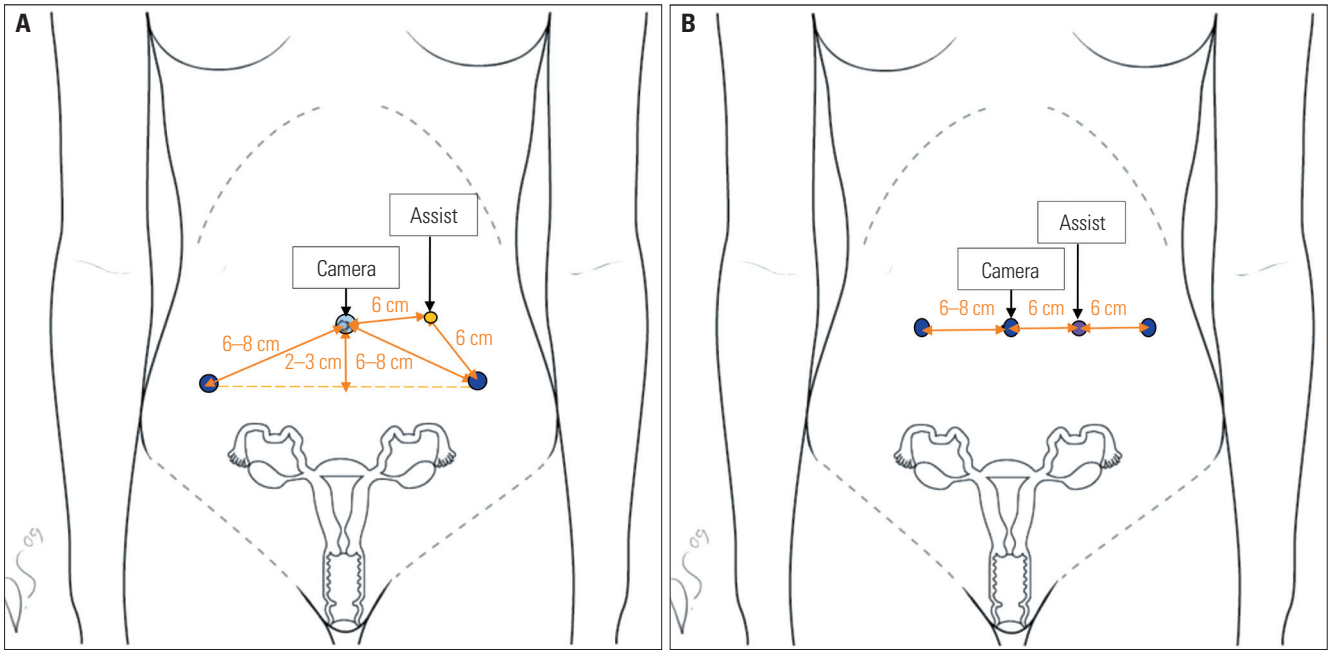

Fig. 1. Port placement in the robot-assisted staging surgery using three robotic arms. A: S/Si model: 3 ports. B: Xi model: 3 ports.

ables: surgical method, age, FIGO stage, histology, grade, and lymph node status. We performed propensity score matching to reduce the bias in the estimate of the difference in survival after open and robot-assisted surgical staging for endometrial cancer. The propensity score model accounted for the surgical stage, grade, and histology. To estimate the difference in survival between the two surgical methods, we constructed a proportional hazards model using the matched data.

RESULTS

Patient characteristics

The flowchart for patient selection is shown in Fig. 2. In total, 423 patients were identified between May 2006 and May 2018; their clinical and pathological characteristics are shown in detail in Table 1. Open surgery was performed in 218 (51.5%)

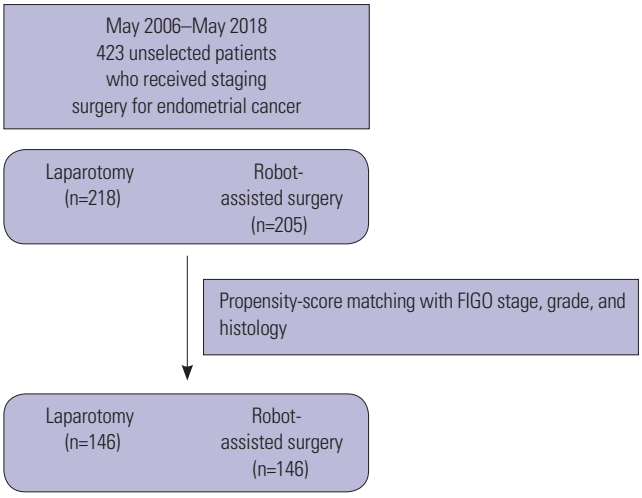

Fig. 2. Flowchart of patient selection. FIGO, Federation of Gynecology and Obstetrics.

Table 1. Patient Characteristics Before and After PSM

Characteristic	Before PSM			After PSM		
	Laparotomy (n=218)	Robotic (n=205)	*p* value	Laparotomy (n=146)	Robotic (n=146)	*p* value
Age (yr)	55.2 (10.2)	52.8 (9.0)	0.080	54.9 (10.2)	53.4 (8.8)	0.850
BMI (kg/m^2)	24.7 (4.8)	24.6 (5.2)	0.880	24.9 (5.1)	24.5 (5.3)	0.340
FIGO stage						
I	138 (63.0)	182 (88.8)	<0.010	124 (84.9)	124 (84.9)	0.990
II	17 (7.8)	5 (2.4)		5 (3.4)	5 (3.4)	
III	42 (19.3)	16 (7.8)		15 (10.3)	15 (10.3)	
IV	21 (9.6)	2 (1.0)		2 (1.4)	2 (1.4)	
Cell type			<0.010			0.990
Endometrioid	147 (67.4)	166 (81.0)		117 (80.1)	117 (80.1)	
Other	71 (32.6)	39 (19.0)		29 (19.9)	29 (19.9)	
Grade			<0.010			0.990
1	73 (33.5)	106 (51.7)		63 (43.2)	63 (43.2)	
2	67 (30.7)	64 (31.2)		51 (34.9)	51 (34.9)	
3	78 (35.8)	35 (17.1)		32 (21.9)	32 (21.9)	
Harvested LN, median (range)						
Pelvic LN	16 (2–54)	12 (2–72)	0.990	16 (2–47)	13 (2–46)	0.180
Paraaortic LN	3 (0–51)	3 (0–36)	0.340	3 (0–35)	3 (0–36)	0.550
EBL (cc)	409.6 (614.4)	91.9 (108.2)	<0.010	316.8 (333.4)	113.0 (113.0)	<0.010
Transfusion	40 (18.3)	11 (5.4)	<0.100	9 (6.2)	6 (4.1)	0.420
Conversion to laparotomy		0			0	
Adjuvant therapy			<0.010			0.020
Radiation	53 (24.3)	27 (13.2)		41 (28.1)	20 (13.7)	
Chemotherapy	62 (28.4)	29 (14.1)		20 (13.7)	23 (15.8)	
Both	22 (10.1)	7 (3.4)		9 (6.2)	6 (4.1)	
None	81 (37.2)	142 (69.3)		76 (52.1)	97 (66.4)	
Recurrence			<0.010			0.380
No	177 (81.2)	187 (91.2)		128 (87.7)	133 (91.1)	
Yes	41 (18.8)	18 (8.8)		18 (12.3)	13 (8.9)	
Vital status			0.120			0.770
Alive	190 (87.2)	193 (94.1)		133 (91.1)	135 (92.5)	
Dead	28 (12.8)	12 (5.9)		13 (8.9)	11 (7.5)	

PSM, propensity score matching; SD, standard deviation; BMI, body mass index; FIGO, International Federation of Gynecology and Obstetrics; LN, lymph node; EBL, estimated blood loss.
Data are presented as mean (SD) or n (%).

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patients, and 205 (48.5%) underwent RSS using three robotic arms. There were no conversions to open laparotomy. After propensity score weighting, 146 patients were matched in each surgical group, and there was no difference in any of the patient characteristics, except for the estimated blood loss (EBL) and the number of adjuvant treatments (Table 1). EBL was significantly higher in the laparotomy group than in the robotic surgery group (316.8 cc vs. 113.0 cc; $p<0.010$), but the number of transfusions did not differ between the two groups. A significant difference was found in the proportion of patients who were treated with adjuvant therapy between the propensity score-matched groups (28.1% in open group vs. 13.7% in robotic group; $p=0.019$). After propensity score weighting, overall, 31 (10.6%) patients experienced recurrence, and there was no difference in this regard between the two groups ($p=0.380$). There were 24 deaths (8.2%) in the entire propensity score-matched cohort, and no difference was observed between the two groups in this regard ($p=0.770$).

Survival outcome

After propensity score matching that accounted for the FIGO stage, grade, and histology, Kaplan-Meier survival analysis showed no significant differences in DFS ($p=0.695$) and OS ($p=0.487$) between the two groups (Fig. 3). The estimated 5-year DFS rates were 86% and 89% in the laparotomy and robot-assisted surgical cohorts, respectively. The estimated 5-year OS rates were 91% and 92% in the laparotomy and robot-assisted surgical cohorts, respectively.

Univariate and multivariate regression analyses

In the univariate regression analyses of the complete cohort with DFS as the endpoint, the mode of surgery, FIGO stage, grade, histology, and lymph node metastasis were associated with increased risk of recurrence, whereas in the following multivariate analysis, only grade 3 ($p<0.010$) was shown to be a significant independent risk factor. When OS was set as the endpoint, the mode of surgery, age, FIGO stage, histology, grade, and lymph node metastasis were significantly associated with worse prognosis in the univariate regression analysis of the complete cohort. In the multivariate analysis, FIGO stage IV ($p<0.01$), histology ($p=0.010$), and grade 3 ($p<0.010$) were found to be significant independent risk factors (Table 2).

DISCUSSION

The present study compared the survival outcomes between open surgery and RSS using three robotic arms in the era of a shift in the standard of care in the surgical management of endometrial cancers from open surgery to MIS. We found that staging surgery using three robotic arms in robotic surgery did not seem to compromise survival outcomes when compared to laparotomy for endometrial cancer. To the best of our knowledge, this is the first study to evaluate the survival outcomes between RSS using three robotic arms and open staging surgery for endometrial cancer. In South Korea, where robotic surgery is not covered by the National Health Insurance, it is necessary to reduce the economic burden on patients, and finding a strategy to reduce cost including using three robotic arms would have clinical implication.

The introduction of robot-assisted laparoscopic surgery has been shown to increase the application of MIS for malignancies,[8,21,22] and MIS has been demonstrated to decrease surgical complications.[23-26] Specifically, robot-assisted surgery is beneficial for obese patients, as it is correlated with a significantly reduced rate of surgical complications than that seen with open surgery, as well as a lower rate of conversion to open surgery when compared with conventional laparoscopy.[27-29] However, in terms of the survival outcomes of MIS for endometrial cancer, most of the available studies compared open surgery with conventional laparoscopy rather than with robotic surgery, and indicated that laparoscopy was a favorable option for patients with endometrial cancer.[4,30,31] In the present study, we compared the survival outcomes between propensity score-matched

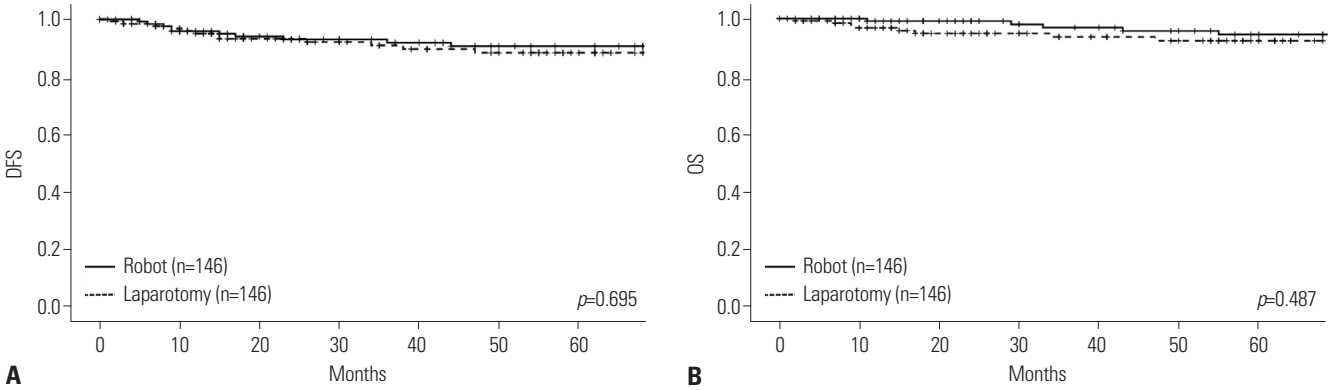

Fig. 3. (A) DFS and (B) OS of the propensity score-matched cohort. Five-year DFSs were 86% and 89% in the open and robot-assisted surgical cohorts, respectively. Five-year OSs were 91% and 92% in the open and robot-assisted surgical cohorts, respectively. DFS, disease-free survival; OS, overall survival.

Table 2. Univariate and Multivariate Analyses of the Complete Cohort (n=423) with DFS and OS as Endpoints

Variables	DFS				OS			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Surgical mode								
Laparotomy	1.00		1.00		1.00		1.00	
Robot	0.43 (0.25–0.76)	<0.001	1.03 (0.56–1.91)	0.901	0.42 (0.21–0.82)	0.010	0.92 (0.42–1.97)	0.830
Age (yr)								
≤49	1.00		1.00		1.00		1.00	
≥50	1.31 (0.72–2.40)	0.360	1.03 (0.56–1.91)	0.192	2.36 (0.99–5.63)	0.052	2.09 (0.85–5.12)	0.103
FIGO stage								
I	1.00		1.00		1.00		1.00	
II	3.85 (1.58–9.41)	<0.001	1.99 (0.21–18.83)	0.543	2.85 (0.83–9.75)	0.087	1.52 (0.07–30.88)	0.780
III	3.633 (1.88–7.01)	<0.001	0.47 (0.50–4.50)	0.831	3.12 (1.34–7.29)	<0.001	0.45 (0.00–25.01)	0.898
IV	19.36 (9.94–37.69)	<0.001	11.51 (5.49–24.14)	<0.001	19.69 (9.20–42.10)	<0.001	11.27 (4.80–26.43)	<0.001
Histology								
Endometrioid	1.00		1.00		1.00		1.00	
Other	3.44 (2.05–5.77)	<0.001	1.44 (0.79–2.63)	0.223	5.60 (2.95–10.61)	<0.001	2.47 (1.17–5.24)	0.012
Grade								
1	1.00		1.00		1.00		1.00	
2	2.16 (0.94–4.95)	0.058	1.82 (0.78–4.23)	0.151	3.11 (0.97–9.92)	0.053	2.62 (0.81–8.44)	0.062
3	7.39 (3.54–15.39)	<0.001	3.68 (1.61–8.39)	<0.001	11.82 (4.11–33.92)	<0.001	4.59 (1.45–14.49)	<0.001
LN metastasis								
Negative	1.00		1.00		1.00		1.00	
Positive	5.36 (3.12–9.20)	<0.001	1.68 (0.69–4.03)	0.122	6.16 (3.22–11.77)	<0.001	1.56 (0.51–4.70)	0.430

DFS, disease-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; LN, lymph node.

groups of patients undergoing open and robotic surgery using three robotic arms after the introduction of robot-assisted laparoscopic surgery. Our results showed that the adoption of robotic surgery did not compromise the survival outcomes, despite the inclusion of the learning curve for all gynecologic oncologists.

In the published literature, few studies have reported results on comparative long-term oncological outcomes between laparotomy and robotic surgery for endometrial cancer due to limited data and short follow-up period. Corrado, et al.[32] observed that the 3-year OS rates were 86.7% and 91.5% and the 3-year DFS rates were 92.1% and 91.5% following open and robotic surgeries, respectively. Likewise, Cardenas-Goicoechea, et al.[33] showed that there were no significant differences in survival between robotic and laparoscopic surgeries (3-year OS: 93.6% and 93.3%, and 3-year DFS: 88.4% and 83.3%, with conventional laparoscopy and robotic surgery, respectively). Moreover, Brudie, et al.[34] reported a 3-year DFS of 89.3% and a 3-year OS of 89.1%, and Kilgore, et al.[35] noted a 5-year OS of 89.1% in patients who underwent robotic surgery for endometrial cancer. Compared with the previous reports, we demonstrated comparable survival outcomes (5-year DFS: 89% and 5-year OS: 92%) in the robotic surgery group when using the equipment with three robotic arms in this study.

The use of three robotic arms is unique, since most other studies on robotic gynecologic surgery used four robotic arms for staging surgery for endometrial cancer. The use of three robotic arms at our institution is mainly due to cost considerations. The highly cost-intensive nature of robotic surgery is a major obstacle in determining the robotic surgical mode and conducting a randomized clinical trial. Currently, the cost for robotic surgery is not reimbursed by the National Health Insurance in South Korea; therefore, patient expenses for robotic surgery are approximately four times higher than that for conventional laparoscopic or open surgery. It has been previously reported that eliminating one robotic arm may allow the patient to save approximately US$500.[18] Since the introduction of the robotic surgical system in our institution, we have used three robotic arms for performing robotic surgeries, and have not encountered or observed major technical difficulties or perioperative complications.

The strength of our study was that all surgical procedures and adjuvant treatments were conducted at a single institution by fellowship-trained gynecologic oncologists and designated radiation oncologists. Despite this strength, our study also had some limitations, including the retrospective nature of the study and unmeasured variables that can cause confounding. In addition, potential selection bias, especially that owing to the selection of patients who can undergo robotic surgery, may also exist. Due to the small sample size, further investigation is cur-

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rently underway to determine whether the main findings of this study are comparable to those obtained when data collected from a large national database are analyzed.

In conclusion, our data suggested that robotic staging surgery using three robotic arms and laparotomy for endometrial carcinoma had equivalent survival outcomes. Long-term follow-up and multicenter investigations are required to confirm the result of this study as well as its generalizability.

AUTHOR CONTRIBUTIONS

Conceptualization: Young Tae Kim. Data curation: Kyung Jin Eoh and Dae Woo Lee. Formal analysis: Kyung Jin Eoh and Dae Woo Lee. Funding acquisition: Young Tae Kim. Investigation: Young Tae Kim. Methodology: Ji Hyun Lee, Eun Ji Nam, and Sang Wun Kim. Project administration: Young Tae Kim. Resources: Young Tae Kim, Eun Ji Nam, and Sang Wun Kim. Software: Kyung Jin Eoh. Supervision: Young Tae Kim. Validation: Sang Wun Kim. Visualization: Eae Woo Lee. Writing—original draft: Kyung Jin Eoh. Writing—review & editing: Young Tae Kim. Approval of final manuscript: all authors.

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