Outcomes and patterns of recurrence of robot-assisted or laparoscopic radical hysterectomy in early-stage cervical cancer

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Abstract. The present study aimed to evaluate the surgical outcomes and prognosis of minimally invasive surgery (MIS), including robot-assisted radical hysterectomy (RARH) and laparoscopic radical hysterectomy (LRH), and open radical hysterectomy (ORH) for the treatment of early stage cervical cancer. A total of 43 patients were enrolled into the ORH group, 14 patients into the LRH group and 21 patients into the RARH group, and the patients were followed up for ≥3 years. Age, body mass index, International Federation of Gynecology and Obstetrics 2008 stage, histology, tumor size, lymphovascular space invasion, lymph node metastasis, number of dissected lymph nodes, operative duration, estimated blood loss, hospitalization duration and complications were reviewed. On follow-up, 16.3% of relapses (7/43) and 11.6% of deaths (5/43) occurred in the ORH group. In the LRH group, 14.3% of patients relapsed (2/14) and no deaths were reported; however, in the RARH group, 33.3% of patients relapsed and 9.5% died (2/21). In patients treated with RARH, >50% of recurrences occurred in distant lesions because of metastasis. No significant difference was found in patient prognosis between the three groups. The difference in 3-year recurrence between the MIS and ORH groups was not statistically significant (MIS vs. ORH, 74.3 vs. 83.7%; log-rank P=0.253). In addition, there was no recurrence in patients with stage IB1 cervical cancer in the RARH group. LRH and RARH were superior to ORH with regard to surgical outcomes, such as estimated blood loss, and therefore may be considered a safe and feasible alternative to ORH. However, RARH would not be an appropriate surgical approach in patients with large tumors and parametrial invasion. In the future, the ideal indications for each surgical procedure should be reassessed, and the significance of the relationship between the difficulty of surgery, such as in cases of bulky tumor, parametrium invasion and vaginal invasion, and disease recurrence should be discussed. In conclusion, MIS could be safe and useful if proper case selection is performed.

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Abbreviations: RARH, robot-assisted radical hysterectomy; LRH, laparoscopic radical hysterectomy; ORH, open radical hysterectomy; ECC, early-stage cervical cancer; FIGO, International Federation of Gynecology and Obstetrics; MIS, minimally invasive surgery

Key words: cervical cancer, RARH, LRH, surgical outcome, prognosis, pattern of recurrence

Introduction

Cervical cancer is the second most common cancer globally, with more than 275,000 deaths and 530,200 new cases in 2010 (1). Approximately 13,000 new cases of cervical cancer were diagnosed in Japan, and an estimated 3,500 women died from this disease (2). Methods for preventing cervical cancer, such as administration of the human papillomavirus (HPV) vaccine and cervical cancer screening with cytology, have developed, in contrast to those for preventing other cancers. However, these measures are not effective in Japan. In June 2013, the HPV vaccine was withdrawn in Japan because of several reports of adverse effects, such as the complex regional pain syndrome, despite the launch of a program encouraging vaccination. Many junior high school students and their parents were concerned about this syndrome, resulting in only a few new vaccinations (0.97%) compared with those prior to these news reports (3,4). Monitoring of cervical cancer was also discontinued, leading to a cancer screening rate of only 28.3% in 2016 (5). Thus, the prevention of cervical cancer in Japan has become difficult, and therefore, the number of patients with early cancer will continue to increase.

Amid the increase in cases with early cervical cancer, the demand for minimally invasive surgery (MIS) such as laparoscopic radical hysterectomy (LRH) and robot-assisted radical hysterectomy (RARH) is expected to increase. In Japan, LRH and RARH were recognized as advanced medical treatments in May and August 2016, respectively. However, MIS suddenly developed an unfavorable impression because of the sensational report of the Laparoscopic Approach to Cervical Cancer (LACC) trial. This was the first trial of early-stage cervical

cancer (ECC) comparing MIS and open radical hysterectomy (ORH) (6). According to the results of this trial, the negative impression of MIS could not be prevented. However, currently, the unsuitability of MIS for radical hysterectomy has little scientific basis. Therefore, this study aimed to compare the surgical outcomes and prognosis of MIS (including RARH and LRH) with ORH performed at a single center, determine the factors related to disease recurrence, such as tumor size and International Federation of Gynecology and Obstetrics (FIGO) 2008 stage, and investigate the specific recurrence pattern of lesions after MIS and the ideal indications of MIS for ECC.

Materials and methods

Patient and tumor characteristics. A total of 78 patients underwent surgery for cervical cancer between December 2008 and January 2019 at the Obstetrics and Gynecology Hospital of Shimane University, Shimane, Japan. Of these, 14 patients underwent LRH, 21 underwent RARH, and 43 underwent ORH (ORH: December 2008 to January 2019, LRH: April 2015 to January 2019, and RARH: July 2015 to January 2019). Radical hysterectomy was performed in patients with FIGO 2008 stage IA1-IIB. Nerve-sparing techniques were attempted in IA2, IB1, and IIA1 cases. The indications for the three methods of hysterectomy were determined based on the criteria of accommodation for cervical cancer in Japan. LRH was performed for stage IA2-IIA, RARH for stage IA2-IIB, and ORH for stage IA2-IIB. During the period of performance of this study, there were no criteria to clarify the effect of cervical tumor size, as determined by endoscopic surgery, on the choice of method of hysterectomy. Therefore, in this study, LRH or RARH was selected regardless of tumor diameter, except for patients older than 75 years and with severe comorbidities.

We analyzed the following parameters in our study: perioperative variables such as age, FIGO 2008 stage, histology, tumor size, lymphovascular space invasion (LVSI), and lymph node metastasis. The surgical outcomes included hospitalization duration, operative duration, estimated blood loss, number of dissected lymph nodes, transfusion rate, conversion to laparotomy, and intraoperative and postoperative complications. The region of recurrence and the period until recurrence were also assessed. Operative duration was defined as the duration between incision and wound closure. Operative duration was defined as console duration only in RARH. Estimated blood loss was the sum of volume of suctioned fluids, weighted gauze minus dry gauze, and other fluids at the end of surgery.

Surgical procedure

Equipment system and electric device. We used the 1588 AIM camera system (Stryker) for LRH and the da Vinci S or Xi Surgical System (Intuitive Surgical Inc.) for RARH. General anesthesia was induced via endotracheal intubation with the patient in a lithotomy-Trendelenburg position. The details of the surgical technique have been described in previous studies. The uterine artery was cut, and the vessels over the ureter were dissected. The bilateral anterior and posterior vesicouterine ligaments were divided and incised. Briefly, for LRH, a 12 mm trocar was inserted through the umbilicus. Two 5 mm lateral trocars were inserted symmetrically 6 cm from the umbilicus below the horizontal line of the umbilicus. Two other 12 mm trocars were inserted bilaterally at the outer third of the iliac spine. For RARH, 5 trocars were used. A 12 mm trocar was placed 3 cm from the umbilicus for the camera. Two 8 mm trocars were placed bilaterally 8 cm from the umbilicus for the three robotic arms. In addition, a 12 mm trocar was placed in the right upper quadrant for assistance.

For LRH, a Harmonic Ace+® device (Ethicon, Cincinnati, Ohio) was used, whereas for RARH, a pair of monopolar scissors (Intuitive Surgical Inc.) and fenestrated bipolar forceps (Intuitive Surgical Inc.) were used. Sometimes, LigaSure™ (Coviden) was used. Pelvic lymphadenectomy was performed and the ureter was separated from the lateral peritoneum.

Method of surgery (lymphadenectomy, nerve-sparing, or vaginal wall incision). The surgical steps were performed as follows: i) pelvic lymphadenectomy, ii) dissection of the uterine artery and deep uterine veins, iii) isolation of the ureter, iv) resection of the round ligament, cardinal ligament, and uterosacral ligament of the uterus, v) nerve sparing technique: identification of the nerve fibers (bladder branches) and their detachment from the vaginal wall, vi) radical separation of the nerve fibers attached to the pelvic side wall, with preservation of all parasympathetic fibers, vii) separation of the parametrium and paracolpium from the uterus and vagina, viii) resection of the anterior and posterior parts of the vesico-vaginal ligament, ix) Incision of the vaginal wall using the transperitoneal approach, and x) repair of the vaginal wound with interrupted sutures.

A nerve-sparing approach was performed for cases with stage IA2-IIA lesions. In all cases, the parametrial tissue was incised 1 to 2 cm from the margin or to one fourth to one third of the vagina for type C radical hysterectomy.

In cases in which LRH and RARH were performed, we used the uterine manipulator. A vaginal cuff was not made in all cases. We removed isolated lymph nodes thorough the abdominal trocar in a bag or using a trocar sleeve.

Survival duration. Survival duration was calculated from the date of initial surgery to the date of last follow-up for patients who were alive or to the date of death for patients who died with evidence of cervical cancer. Recurrence duration was calculated from the date of first treatment to the date of last follow-up for patients who were diagnosed with recurrent cervical cancer.

Statistical analysis. Statistical calculations were performed using Statistical Package for Social Sciences 23.0 (SPSS Inc.). One-way analysis of variance followed by Tukey's post hoc test, and Kruskal-Wallis test followed by Dunn's post hoc test were used for parametric and non-parametric variables, respectively. Differences between proportions were compared using Fisher's exact test or χ^2 test. Differences between ORH and MIS were evaluated using Fisher's exact test. Among patients who underwent radical hysterectomy and were followed up for more than 3 years, progression-free survival (PFS) and overall survival (OS) were calculated using the Kaplan-Meier method with the log-rank test. A multivariate logistic regression model was used to evaluate the association between outcome and exposure. The hazard ratio was calculated for binary data

Table I. Patients' characteristics.

Variable	RH (n=43)	LRH (n=14)	RARH (n=21)	P(ORH/LRH)	P(ORH/RARH)	P(LRH/RARH)
Age, years	56.8	47.4	51	0.026	0.098	0.373
BMI, kg/m^2	22.4	21	21.6	0.123	0.248	0.594
FIGO stage, n (%)						
IA1	0 (0.0)	0 (0.0)	0 (0.0)			
IA2	1 (2.3)	1 (7.1)	0 (0.0)			
IB1	16 (37.2)	10 (71.4)	11 (52.4)			
IB2	7 (16.3)	1 (7.1)	4 (19.0)			
IIA1	2 (4.7)	1 (7.1)	1 (4.8)			
IIA2	3 (7.0)	1 (7.1)	0 (0.0)			
IIB	14 (32.6)	0 (0.0)	5 (23.8)			
Histology, n (%)						
Adenocarcinoma	8 (18.6)	4 (28.6)	9 (50.0)			
Adenosquamous cell carcinoma	3 (7.0)	0 (0.0)	1 (0.0)			
Squamous cell carcinoma	32 (74.4)	10 (71.4)	11 (50.0)			
Tumor size, n (%)						
<4 cm	17 (39.5)	13 (92.9)	13 (61.9)			
≥4 cm	26 (60.5)	1 (7.1)	8 (38.1)			
Tumor size, cm	44.4	22.5	29.7	0.001	0.008	0.174
Infiltration depth of cervical tumor, n (%)						
No infiltration	2 (4.7)	4 (28.6)	2 (9.5)			
Superficial	9 (20.9)	5 (35.7)	6 (28.6)			
Deep muscular	31 (72.1)	4 (28.6)	13 (61.9)			
N/A	1 (2.3)	1 (7.1)	0			
Metastasis, n (%)						
Pelvic lymph node	15 (34.9)	0 (0.0)	5 (23.8)			
Lymphovascular space invasion n(%)	31 ()	7 (50.0)	13 ()			
N/A	4 ()	1 (7.1)	0			

ORH, open radical hysterectomy; LRH, laparoscopic radical hysterectomy; RARH, robot-assisted radical hysterectomy; FIGO, International Federation of Gynecology and Obstetrics.

with a confidence interval of 95%. P<0.05 was considered to indicate a statistically significant difference.

Results

Patient and tumor characteristics. Patient demographics are shown in Table I. We determined that 37.2, 71.4, and 52.4% of patients who underwent ORH, LRH, and RARH, respectively, had FIGO 2008 stage IB1 disease. Additionally, 32.6% of patients in the ORH and 20.0% of patients in RARH group had FIGO 2008 stage IIB disease. Regarding the histological analysis of cancerous tissue, adenocarcinoma was evident in 19.6, 28.6, and 50.0% of patients in the ORH, LRH, and RARH groups, respectively. The mean tumor size was 44.4 mm in the ORH, 22.5 mm in the LRH, and 29.7 mm in the RARH groups. There were statistically significant differences in these factors between ORH and LRH, and ORH and RARH groups. In the ORH and RARH groups, deep vascular infiltration of the cervical stroma was evident in approximately 60.0-70.0% of patients, compared with 28.6% of patients in the LRH group. Metastasis of pelvic lymph nodes was found in 34.9 and 23.8% of patients in the ORH and RARH groups, respectively. In the LRH group, no patient had metastasis to the pelvic lymph nodes. There was a statistically significant difference in age between the ORH and LRH (P=0.026) and in tumor size between the ORH and MIS (LRH+RARH) groups. Other factors were not significantly different between the groups.

Surgical outcomes. As shown in Table II, preparation duration, operative duration, estimated blood loss, number of dissected lymph nodes, hospitalization duration, and amount of transfused blood were compared between groups. The mean operative duration for RARH was significantly longer than that for ORH and LRH [(PORH/RARH) <0.0001 and P(LRH/RARH)=0.014]. The mean estimated blood loss was significantly less in the MIS groups [P(ORH/LRH) <0.0001 and P(ORH/RARH) <0.0001]. The mean hospitalization duration was also significantly less in the LRH group [P(ORH/LRH) <0.0001]. No statistically

Table II. Surgical outcomes and operating findings.

Variable	ORH (n=43)	LRH (n=14)	RARH (n=21)	P(ORH/LRH)	P(ORH/RARH)	P(LRH/RARH)
Operative time, min	330.2±75.3	353.5±52.5	435.4±90.6	0.113	<0.0001	0.014
Estimated blood loss, ml	1,212.2±820.8	250.7±272.0	241.2±237.6	<0.0001	<0.0001	0.913
Hospitalization, days	25.3±22.8	10.8±3.0	16.64±17.2	<0.0001	0.128	0.225
Blood transfusion, n (%)	13 (28.3)	1 (7.1)	2 (10.0)			
Lymph nodes counted, n	33.5±12.5	33.4±9.5	42.5±16.3	0.517	0.017	0.184
Conversion to laparotomy, n (%)		0 (0.0)	0 (0.0)			
Follow-up visit result, n(%)						
No relapse	36 (83.7)	12 (85.7)	14 (66.7)			
Relapse	7 (16.3)	2 (14.3)	7 (33.3)			
Death	5 (11.6)	0 (0.0)	2 (9.5)			
Intra- or post-operation complications, n (%)	2 (4.7)	2 (14.3)	2 (9.5)			

Data presented as mean ± SD, unless otherwise specified. ORH, open radical hysterectomy; LRH, laparoscopic radical hysterectomy; RARH, robot-assisted radical hysterectomy.

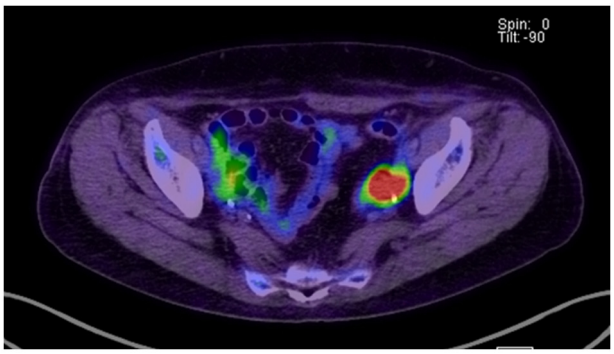

Figure 1. Pattern of disease recurrence. Disseminated lesion on the surface of the left iliopsoas muscle.

significant differences were found in the number of dissected lymph nodes between the groups. Intraoperative complications were observed in all groups. In the ORH group, 2 cases of bladder injury occurred. In the LRH group, one case of bladder injury and one case of vessel injury occurred. These injuries were repaired immediately during surgery. In the RARH group, one case of ureteral injury and one case of rectal injury occurred. Of the 35 cases, no case required conversion from laparoscopy to laparotomy. Further, no case in the RARH group needed a switch to conventional laparoscopy. All patients had an uncomplicated postoperative course.

Pattern of recurrence. The detailed pattern of recurrence for each procedure is shown in Table III and Fig. 1. Patients in the ORH group had several patterns of disease recurrence. Patients in the LRH group treated without adjuvant therapy had local recurrence. In the RARH group, intraperitoneal dissemination was found in two cases, which could be a specific pattern in RARH (Fig. 1). These two patients had large tumors. In case 11, disseminated lesions in the peritoneal cavity and port site were observed. In case 12, a disseminated lesion on the surface of the left iliopsoas muscle was observed (Fig. 1). However, it should be noted that no patients with stage IB1 disease who underwent RARH exhibited recurrence (Table IV).

Oncologic outcomes. PFS and OS were not significantly different between the surgical procedures (Figs. 2 and 3). The 3-year PFS was 74.3% in the MIS group and 83.7% in the ORH group (log-rank P=0.253) (Fig. 2A). The 3-year OS was 91.4% in the MIS group and 88.4% in the ORH group (log-rank P=0.682) (Fig. 2B). More specifically, the 3-year PFS was 85.7, 66.7, and 83.7% in the LRH, RARH, and ORH groups, respectively [log-rank P(ORH/LRH)=0.861, P(ORH/RARH)= 0.077, and P(LRH/RARH)=0.192] (Fig. 3A). The 3-year OS was 100.0, 85.7, and 88.4% in the LRH, RARH, and ORH groups, respectively [log-rank P(ORH/LRH)=0.189, P(ORH/RARH)= 0.671, and P(LRH/RARH)=0.081] (Fig. 3B). There was no statistically significant difference in PFS or OS between surgical procedures; however, the survival tended to be shorter with MIS. Furthermore, in patients with stage IB1 disease, the prognosis of MIS was not inferior to that of ORH (Fig. S1A and B).

Cox univariate and multivariate regression analyses were performed for PFS and OS (Table VA and B) including known risk factors for survival such as histology, FIGO 2008 stage, lymph node metastasis, LVSI, and depth of invasion and surgical factors such as operative duration and estimated blood loss. Univariate analysis revealed that elderly patients, those with lymph node metastasis, and those with higher than stage IB2 disease were more prone to disease recurrence. Long operative duration was also related to disease recurrence. Multivariate analysis revealed that age, FIGO 2008 stage, depth of invasion, and operative duration were risk factors for disease recurrence. Furthermore, MIS was not proven to be a factor for shortened PFS. The relationship between OS and recurrence factors was similar to that between PFS and recurrence factors (Table VB).

Table III. Pattern of recurrence in each surgical procedure.

Case	Surgery	Age, years	FIGO stage	pT	Tumor size, mm	Histology	LN metastasis	LVSI	Infiltration on depth of cervical tumor, %	Adjuvant therapy	Recurrence region	Recurrence interval, months
1	ORH	75	IIA1	pT2a1	9	Adeno	(+)	(+)	70	RT	Vaginal stump, pelvic lymph node	9
2	ORH	34	IB1	pT1b1	25	Adeno	(+)	(+)	80	CCRT	Paraaortic LN, liver, meninges	3
3	ORH	81	IB1	pT1b2	45	SCC	(-)	(+)	40	RT	Stump, pelvic lymph node	12
4	ORH	74	IIB	pT2b	85	Adeno-squamous	(+)	(+)	100	CCRT	Pelvic lymph node	42
5	ORH	69	IIB	pT2b	65	SCC	(+)	(+)	100	CCRT	Stump, pelvic lymph node	8
6	ORH	52	IIB	pT2b	63	SCC	(-)	(+)	100	CCRT	Pelvic lymph node	3
7	ORH	77	IIA2	pT2a2	50	Adeno	(+)	(+)	69	(-) rejected	Pelvic lymph node	2
8	LRH	64	IB1	pT1b1	30	SCC	(-)	(+)	40	(-)	Stump, pelvic lymph node	10
9	LRH	66	IIA1	pTis	(-)	SCC	(-)	(-)	0	(-)	Stump	17
10	RARH	68	IIA1	pT1a1	2.6	SCC	(-)	(-)	(-)	(-)	Stump, pelvic lymph node	7
11	RARH	40	IB2	pT1b2	55	Adeno	(-)	(+)	90	CCRT	Intraperitoneal dissemination	24
12	RARH	44	IB2	pT1b2	72	Adeno-squamous	(-)	(+)	90	CCRT	Surface of left iliopsoas muscle	4
13	RARH	60	IIB	pT2b	42	Adeno	(+)	(+)	100	CCRT	Lung, pelvic lymph node	5
14	RARH	59	IIB	pT2b	45	SCC	(+)	(+)	80	CCRT	Mediastinal lymph node	30
15	RARH	61	IIB	pT2b	45	SCC	(+)	(+)	100	CT	Lung, pelvic lymph node	5
16	RARH	61	IIB	pT2b	25	SCC	(+)	(+)	80	CT	Pelvic lymph node	4

ORH, open radical hysterectomy; LRH, laparoscopic radical hysterectomy; RARH, robot-assisted radical hysterectomy; FIGO, International Federation of Gynecology and Obstetrics; LN, lymph node; LVSI, lymphovascular space invasion; SCC, squamous cell carcinoma; Adeno, adenocarcinoma; RT, radiotherapy; CCRT, concurrent chemoradiotherapy; CT, chemotherapy.

Table IV. Patient characteristics in RARH group.

Age, years	FIGO stage	pT	Tumor size, mm	Histology	LN metastasis	LVSI	Infiltration depth of cervical tumor, %	Adjuvant therapy	Recurrence	Site of recurrence
35	IB1	IB1	37	Adeno	(-)	(+)	80	CCRT	(-)	(-)
43	IB1	IB1	23	Adeno	(-)	(+)	45	CCRT	(-)	(-)
56	IB1	IB1	12	Adeno	(-)	(-)	20	CCRT	(-)	(-)
49	IB1	IB1	4	Adeno	(-)	(-)	10	(-)	(-)	(-)
57	IB1	IB1	8	SCC	(-)	(-)	0	(-)	(-)	(-)
50	IB1	IB1	4	Adeno	(-)	(-)	0	(-)	(-)	(-)
53	IB1	IB1	20	Adeno	(-)	(+)	55	CCRT	(-)	(-)
43	IB1	IB1	35	Adeno	(-)	(+)	25	CCRT	(-)	(-)
39	IB1	IB1	10	Adeno	(-)	(-)	10	CCRT	(-)	(-)
54	IB1	IB1	15	SCC	(-)	(+)	55	CCRT	(-)	(-)
37	IB1	IB1	18	SCC	(-)	(-)	100	CCRT	(-)	(-)
40	IB2	IB2	55	Adeno	(-)	(+)	90	CCRT	(+)	Surface of left iliopsoas muscle
44	IB2	IB2	72	Adeno	(-)	(+)	90	CCRT	(+)	Peritoneal dissemination
55	IB2	IB2	43	Adeno	(-)	(-)	25	CCRT	(-)	(-)
32	IB2	IB2	45	SCC	(-)	(+)	95	CCRT	(-)	(-)
68	IIA1	IA1	22	SCC	(-)	(-)	20	(-)	(+)	Stump, pelvic lymph node
59	IIB	IIB	45	SCC	(+)	(+)	80	CCRT	(+)	Mediastinal lymph node
60	IIB	IIB	42	Adeno	(+)	(+)	100	CCRT	(+)	Lung, pelvic lymph node
61	IIB	IIB	45	SCC	(+)	(+)	100	TC	(+)	Lung, pelvic lymph node
61	IIB	IIB	25	SCC	(+)	(+)	80	TC	(+)	Pelvic lymph node
74	IIB	IIB	43	SCC	(+)	(+)	81	RT (rejected CCRT)	(-)	(-)

FIGO, International Federation of Gynecology and Obstetrics; LN, lymph node; LVSI, lymphovascular invasion; SCC, squamous cell carcinoma; Adeno, adenocarcinoma; RT, radiotherapy; CCRT, concurrent chemoradiotherapy; CT, chemotherapy.

Discussion

We analyzed the following parameters in our study: perioperative variables such as age, FIGO stage 2008, histology, tumor size, depth of invasion, and metastasis. Intraoperative factors were operative duration, estimated blood loss, blood transfusion, number of dissected lymph nodes, and conversion to laparotomy. Postoperative variables included complications, hospitalization duration, and follow-up results. The results of this study suggest that RARH and LRH are superior to ORH with regard to surgical outcomes and may be safe and feasible alternatives to ORH. The operative duration was acceptable. However, disease recurrence was found to be associated with FIGO 2008 stage-IB2 in the RARH group (Table IV). Further, a long operative duration tended to lead to disease recurrence (Table VA).

We observed two major findings in this study. First, this single-center retrospective study indicated that the risk of disease recurrence was highly associated with the diameter of the tumor and FIGO 2008 stage. Locally advanced cases, such as those with stage IB2 and stage IIB disease, were prone for recurrence in every group. However, no recurrence was observed in patients with stage IB1 cervical cancer in the RARH group. These facts indicate that one reason of recurrence is cancer cell spillage, which would influence the decision to perform radical hysterectomy. RARH is an appropriate surgical approach for patients with cervical cancers having unfavorable outcomes because of large tumor size and/or parametrium invasion. Furthermore, patients with large tumors in the RARH group had specific sites of intraperitoneal recurrence (Fig. 1). We should reassess the ideal

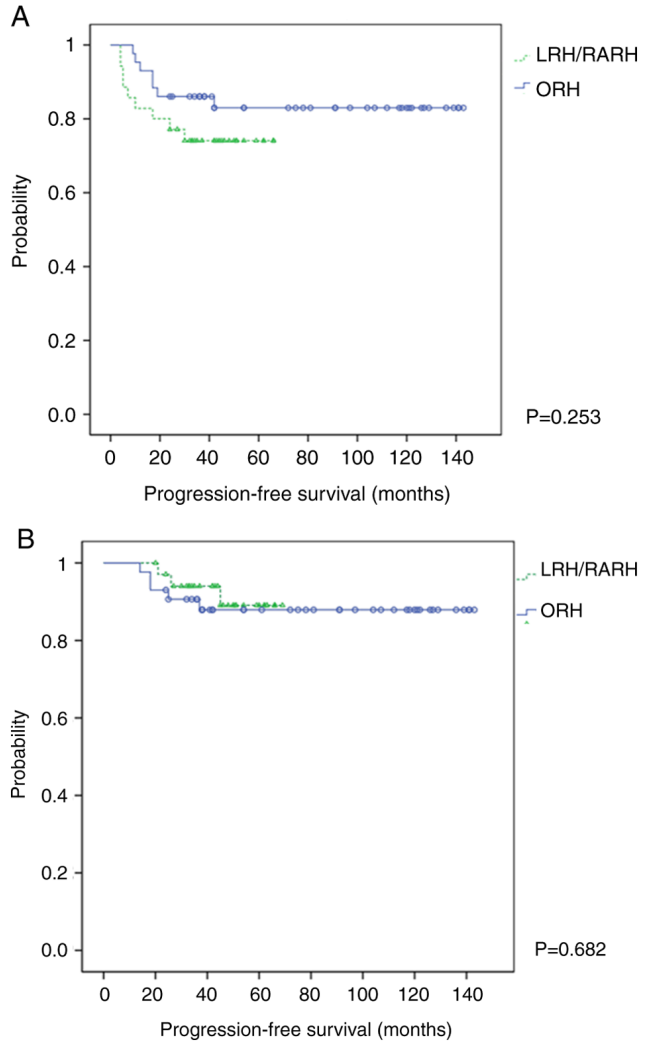

Figure 2. Kaplan-Meier survival analysis to show the differences in 3-year recurrence between ORH and MIS. (A) The 3-year PFS of 74.3% in patients undergoing MIS vs. 83.7% in those undergoing ORH (log-rank P=0.253) ORH, open radical hysterectomy; MIS, minimally invasive surgery. (B) The 3-year OS of 91.4% in the MIS cohort vs. 88.4% in the ORH cohort (log-rank P=0.682). PFS, progression-free survival; OS, overall survival; RARH, robot-assisted radical hysterectomy; LRH, laparoscopic radical hysterectomy; ORH, open radical hysterectomy; MIS, minimally invasive surgery.

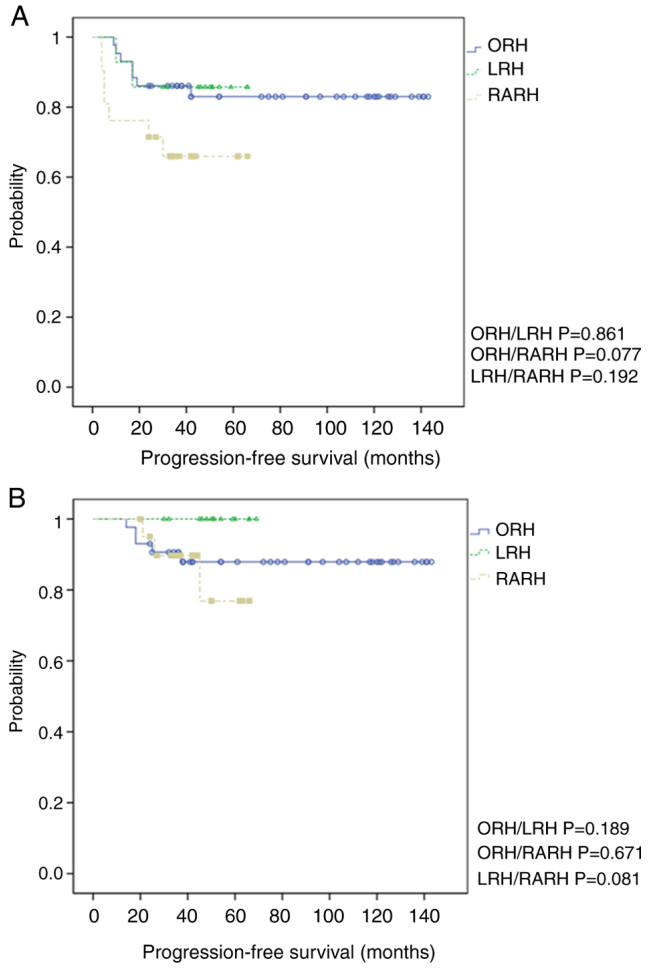

Figure 3. Kaplan-Meier survival analysis demonstrating the difference in 3-year recurrence between ORH, LRH, and RARH cohorts. (A) The 3-year PFS of 85.7, 66.7, and 83.7% in patients treated using LRH, RARH, and ORH [log-rank P(ORH/LRH)=0.861, P(ORH/RARH)=0.077, and P(LRH/RARH)=0.192, respectively]. (B) The 3-year OS of 100.0, 85.7, and 88.4% in patients treated using LRH, RARH, and ORH [log-rank P(ORH/LRH)=0.189, P(ORH/RARH)=0.671, and P(LRH/RARH)=0.081, respectively]. PFS, progression-free survival; OS, overall survival; RARH, robot-assisted radical hysterectomy; LRH, laparoscopic radical hysterectomy; ORH, open radical hysterectomy; MIS, minimally invasive surgery.

indications for each surgery and discuss the significance of the relationship between the difficulty of surgery and disease recurrence.

According to the results of previous studies, MIS is more favorable for the treatment of cervical cancer than ORH. Because of the recent progress in gynecologic laparoscopic technology, LRH has become a preferred surgical method worldwide (7). In addition, since the Food and Drug Administration approved the Da Vinci surgical system for gynecologic procedures in 2007, RARH has gained popularity for the treatment of invasive cervical cancer (8). RARH has been accepted for the treatment of ECC (9,10). RARH has also been associated with better surgical outcomes (11). However, the results of the LACC trial (6) affected the application of RARH in Japan. Institutions as well as the front office of the Japanese Society of Obstetrics and Gynecology redefined the indications for MIS and procedures for prevention of local disease recurrence, such as creating a vaginal cuff and complete removal of tumors and lymph nodes. After the report of the LACC trial, the number of studies questioning the use of MIS increased (12-14). The results of the LACC trial might have been reliable, but every report published following the LACC trial cannot be considered reliable. Several of these reports were published to demonstrate the disadvantages of MIS; however, many questions remain unanswered. Recently, several reports have shown that MIS is an acceptable surgical procedure for small tumors (15-18). Wiebrend and Tjalma (19) also questioned the tendency to avoid MIS in every ECC case. They argued that medical professionals can justify this approach and that surgery should be tailored and performed according to individual patient needs and demands. In the current study, we observed that disease recurrence can be prevented in small tumors such as stage IB1 tumors even with the use of a uterine manipulator and without a vaginal cuff for all cases. This shows that tumor diameter is a more significant

Table V. Univariate and multivariate analysis of survival using a Cox proportional hazards model in patients with cervical carcinoma.

A, Progression-free survival

Factor	Patients (n=78)	Univariate analysis			Multivariate analysis		
		HR	95% CI	P-value	HR	95% CI	P-value
Age, years							
<60	49	0.157	0.050-0.487	0.001	0.105	0.023-0.477	0.004
≥60	29	ref.				ref.	
FIGO stage							
≤IB1	39	0.117	0.027-0.518	0.005	0.02	0.001-0.346	0.007
≥IB2	39	ref.				ref.	
Pelvic lymph node metastasis							
Negative	58	0.284	0.106-0.758	0.012	0.182	0.030-1.119	0.066
Positive	20	ref.				ref.	
Pathological subtype							
SCC	53	0.863	0.314-2.374	0.775	0.494	0.148-1.648	0.251
Non-SCC	25	ref.				ref.	
LVSI metastasis							
No	22	0.324	0.073-1.436	0.138	0.105	0.007-1.706	0.113
Yes	51	ref.				ref.	
Infiltration depth of cervical tumor, %							
<50	28	0.466	0.150-1.445			ref.	
≤50	48	ref.		0.186	35.723	1.846-691.388	0.018
Operation time, min							
<400	56	0.25	0.093-0.672	0.006	0.059	0.010-0.344	0.002
≥400	22	ref.				ref.	
Blood loss, ml							
<500	37	ref.				ref.	
≥500	41	2.182	0.792-6.010	0.131	3.598	0.496-26.094	0.205
Operation							
ORH	43	0.568	0.211-1.525	0.262		ref.	
LRH/RARH	35	ref.			1.305	0.122-13.948	0.826

B, Overall survival

Factor	Patients (n=78)	Univariate analysis			Multivariate analysis		
		HR	95% CI	P-value	HR	95% CI	P-value
Age, years							
<60	49	0.173	0.035-0.859	0.032	0.402	0.065-2.477	0.326
≥60	29	ref.				ref.	
FIGO stage							
≤IB1	39	0.122	0.0015-0.998	0.05	0.063	0.002-2.128	0.123
≥IB2	39	ref.				ref.	
Pelvic lymph node metastasis							
Negative	58	0.175	0.042-0.736	0.017	0.166	0.018-1.489	0.109
Positive	20	ref.				ref.	

Table V. Continued.

B, Overall survival

Factor	Patients (n=78)	Univariate analysis			Multivariate analysis		
		HR	95% CI	P-value	HR	95% CI	P-value
Pathological subtype							
SCC	53	0.336	0.126-2.301	0.505	0.416	0.062-2.807	0.368
Non-SCC	25	ref.				ref.	
LVSI metastasis							
No	22	0.027	0.000-20.578	0.285	NA	NA	NA
Yes	51	ref.					
Infiltration depth of cervical tumor, %							
<50	28	0.198	0.024-1.615	0.131		ref.	
≥50	48	ref.			15.008	0.283-795.880	0.181
Operation time, min							
<400	56	0.392	0.098-1.568	0.186	0.049	0.003-0.856	0.039
≥400	22	ref.				ref.	
Blood loss, ml							
<500	37	ref.				ref.	
≥500	41	2.07	0.494-8.681	0.32	9.531	0.663-137.083	0.097
Operation							
ORH	43	ref.				ref.	
LRH/RARH	35	1.384	0.331-5.796	0.656	31.943	0.465-2193.066	0.108

ORH, open radical hysterectomy; LRH, laparoscopic radical hysterectomy; RARH, robot-assisted radical hysterectomy; FIGO, International Federation of Gynecology and Obstetrics; LN, lymph node; LVSI, lymphovascular space invasion; SCC, squamous cell carcinoma.

factor affecting disease recurrence after MIS than the surgical procedure itself. Of course, cancer cell spillage should be minimized, but not using a uterine manipulator or making a vaginal cuff for small tumors does not ensure prevention of cancer cell spillage. This is because a uterine manipulator ensures a safe operation.

We should reassess the ideal indications for each surgery. It is more important to decide whether to choose MIS or open laparotomy for large tumors.

The strength of our study is the fact that it is a retrospective study performed at a single institution, which unified several treatment decisions, such as selecting the treatment modality, surgical procedure, and post-treatment follow-up. Because of the uniformity in treatment methods, patient prognosis is expected to be more accurate.

However, there are some limitations to our study. First, as mentioned earlier, this study was conducted in a single center; therefore, the number of cases was not sufficient for several statistical analyses. A large number of cases are needed for an accurate analysis. Second, it was difficult to standardize the use of adjuvant therapy. Some cases could not be treated with adjuvant therapy because of the patients' wishes. Two cases that exhibited local recurrence in the LRH group required radiotherapy after surgery because of vaginal invasion or LVSI. If they were treated properly, local recurrence would be prevented. Third, this study applied an approach based on country-specific recommendations; therefore, the findings cannot be extrapolated to women with cervical cancer worldwide. Until now, patients with ECC were undergoing radical hysterectomy and having favorable outcomes in Japan, though these patients would have been treated with concurrent chemoradiotherapy in other countries. The surgical approach for large tumors may not be acceptable in other countries. Forth, in the present study, the choice of surgical method of hysterectomy was not dependent on tumor diameter. However, larger tumors were mostly included in the ORH group, which may have affected the prognostic evaluation. A stratification method could have been considered to avoid such a bias, but the small number of cases did not allow for prognostic analysis in the group with larger tumors; we will address this in a future study. Instead, prognostic analysis was performed using the Kaplan-Meier method for the group with smaller tumors, such as stage IB1 tumors, and showed no significant difference in prognosis depending on the type of hysterectomy performed (Fig. S1A and B).

Finally, all patients treated with MIS would benefit from no recurrence and minimal invasiveness. Laparotomy should be avoided for patients unless the clinician suspects a possibility of recurrence. At the same time, procedures used worldwide to prevent cancer cell spillage should be shared

and learnt. Through this research and similar studies that have been reported in recent years, it can be concluded that preventing cancer cell spillage and operating small tumors using MIS is probably safe and will be associated with a better prognosis. Therefore, we must acquire more knowledge about surgical assessment for MIS by conducting more studies, including a large clinical study with new candidates for surgery and new methods of prevention for disease recurrence. These methods can be useful for obtaining better outcomes for these patients.

This study demonstrated that MIS provided good short-term surgical outcomes. Kaplan-Meier analyses showed no significant difference in prognosis between MIS and open surgery; however, there were some specific recurrence patterns in patients after MIS. We suggest that MIS is a safe and useful procedure if proper case selection is ensured.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

MI designed the study, diagnosed the patients, collected and analyzed clinical data, and drafted the manuscript. KN designed the study, collected and analyzed clinical data, gave advice and drafted the manuscript, as well as performing the final revision. TI collected and analyzed clinical data. HY collected and analyzed clinical data. SS collected and analyzed clinical data. SR drafted the manuscript and analyzed clinical data. SK designed the study, advised on manuscript preparation and revised the final manuscript. MI and SR confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

This study protocol was approved by the Institutional Ethics and Research Review Board at Shimane University (IRB No. 20191120-1; Izumo, Japan). The need for individual patient consent for this retrospective analysis was waived. Patients could opt out at any moment from the study using the opt-out option on the hospital website.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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