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Original Article

Impact of the Learning Curve on the Survival of Abdominal or Minimally Invasive Radical Hysterectomy for Early-Stage Cervical Cancer

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Purpose The objective of this study was to define the learning curve required to attain satisfactory oncologic outcomes of cervical cancer patients who were undergoing open or minimally invasive surgery for radical hysterectomy, and to analyze the correlation between the learning curve and tumor size.

Materials and Methods Cervical cancer patients (stage IA-IIA) who underwent open radical hysterectomy (n=280) or minimal invasive radical hysterectomy (n=282) were retrospectively reviewed. The learning curve was evaluated using cumulative sum of 5-year recurrence rates. Survival outcomes were analyzed based on the operation period ("learning period," P1 vs. "skilled period," P2), operation mode, and tumor size.

Results The 5-year disease-free and overall survival rates between open and minimally invasive groups were 91.8% and 89.0% (p=0.098) and 96.1% and 97.2% (p=0.944), respectively. The number of surgeries for learning period was 30 and 60 in open and minimally invasive group, respectively. P2 had better 5-year disease-free survival than P1 after adjusting for risk factors (hazard ratio, 0.392; 95% confidence interval, 0.210 to 0.734; p=0.003). All patients with tumors < 2 cm had similar 5-year disease-free survival regardless of operation mode or learning curve. Minimally invasive group presented lower survival rates than open group when tumors ≥ 2 cm in P2. Preoperative conization improved disease-free survival in patients with tumors ≥ 2 cm, especially in minimally invasive group.

Conclusion Minimally invasive radical hysterectomy required more cases than open group to achieve acceptable 5-year disease-free survival. When tumors ≥ 2 cm, the surgeon's proficiency affected survival outcomes in both groups.

Key words Uterine cervical neoplasms, Minimally invasive surgical procedures, Learning curve

Introduction

Radical hysterectomy with lymphadenectomy was considered the standard surgical treatment for early-stage cervical cancer for over 100 years [1]. Over the past 20 years, surgical practice shifted from the traditional abdominal approach to minimally invasive surgery. With regard to the surgical outcomes of minimally invasive surgery, various studies directed by multiple institutions showed that minimally invasive surgery was associated with reduced blood loss, shorter hospital stays, and fewer postoperative complications compared to open surgery [2-6].

Nevertheless, survival outcomes of radical hysterectomy were inconsistent in recent studies. Several retrospective studies demonstrated that disease-free survival of minimally invasive radical hysterectomy and open radical hysterectomy was comparable [7-11]. However, in a clinical trial for Laparoscopic Approach to Cervical Cancer, Ramirez et al. [12] reported that the survival rates of minimally invasive radical hysterectomy were lower than those of open radical hysterectomy in cervical cancer.

Several reports have measured surgeon's proficiency, designated as learning curve, in terms operation time [13-15] but there is little report measuring learning curve of minimally invasive radical hysterectomy with regard to survival outcomes. Therefore, we design the study on the learning curve of open radical hysterectomy and minimally invasive radical hysterectomy in terms of recurrence rates. In addition, tumor size is a well-known important survival and prognostic factor of cervical cancer. In the modified International Federation of Gynecology and Obstetrics (FIGO) staging (2018), IB stage was further divided with every 2 cm increase in size into IB1 (< 2 cm), IB2 (2-3.9 cm), and IB3 (≥ 4 cm).

These findings led us to reevaluate the impact of operation mode and tumor size on patients with cervical cancer treated by radical hysterectomy. Hence, in this single-center

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Table 1. Characteristics of early-stage cervical cancer patients (n=562)

Characteristic	Open surgery (n=280)	Minimally invasive surgery (n=282)	p-value
Age, median (range, yr)	48 (18-81)	47 (22-75)	0.427
Body mass index (kg/m²)			
< 24	174 (62.1)	185 (65.6)	0.393
≥ 24	106 (37.9)	97 (34.4)	
Invasion depth (cm)			
≤ 1	201 (71.8)	226 (80.1)	0.020
> 1	79 (28.1)	56 (19.9)	
Tumor size (cm)			
< 2	113 (40.4)	136 (48.2)	0.062
≥ 2	167 (59.6)	146 (51.8)	
Histologic type			
Squamous cell	192 (68.6)	176 (62.4)	0.336
Adenocarcinoma	69 (24.6)	89 (31.6)	
Adenosquamous	13 (4.6)	11 (3.9)	
Others	6 (2.1)	6 (2.1)	
FIGO stage			
IA	28 (10.0)	27 (9.6)	0.005
IB1	190 (67.9)	221 (78.4)	
IB2-IIA	62 (22.1)	34 (12.1)	
Lympho-vascular space invasion	185 (66.1)	97 (34.4)	0.122
Resection margin involvement	21 (7.5)	12 (4.3)	0.102
Dissected lymph node number, mean±SD			
Pelvic LN	23±10	16±10	< 0.001
Para-aortic LN	2±3	1±4	< 0.001
Lymph node metastasis	44 (15.7)	18 (6.4)	< 0.001
Postoperative adjuvant treatment			
No	165 (58.9)	210 (74.5)	< 0.001
Yes	115 (41.1)	72 (25.5)	
Operation type			
Type II radical hysterectomy	26 (9.3)	19 (6.7)	0.281
Type III radical hysterectomy	254 (90.7)	263 (93.3)	
Parametrial involvement	10 (3.6)	6 (2.1)	0.323

Values are presented as number (%) unless otherwise indicated. FIGO, International Federation of Gynecology and Obstetrics Clinical Staging of Cervical Carcinoma; LN, lymph node; SD, standard deviation.

retrospective study with a large number of patients and long follow-up durations, we compared the survival outcomes of patients with early-stage cervical cancer undergoing minimally invasive or open radical hysterectomy and further analyzed the effects of learning curve and tumor size on survival outcomes.

Materials and Methods

1. Study population and data collection

In this study, the records of patients with stage IA-IIA cervical cancer between 2002 and 2018 were retrospectively reviewed. Exclusion criteria were as follows: (1) underwent trachelectomy, type I hysterectomy or underwent only both pelvic lymph node dissection; (2) received neoadjuvant chemotherapy; (3) FIGO stage IA1 without lympho-vascular space invasion (S1 Fig.). In total, 562 patients were eligible for analysis. All the procedures were performed by six gynecological oncologists. A period of time before and after reaching the learning curve was defined as P1 (learning period) and P2 (skilled period). All the surgeons began with open surgery and gradually switched to minimally invasive surgery as experience accumulated. All minimally invasive radical hysterectomy was consecutively collected from the first case of each physician. Surgical procedures included

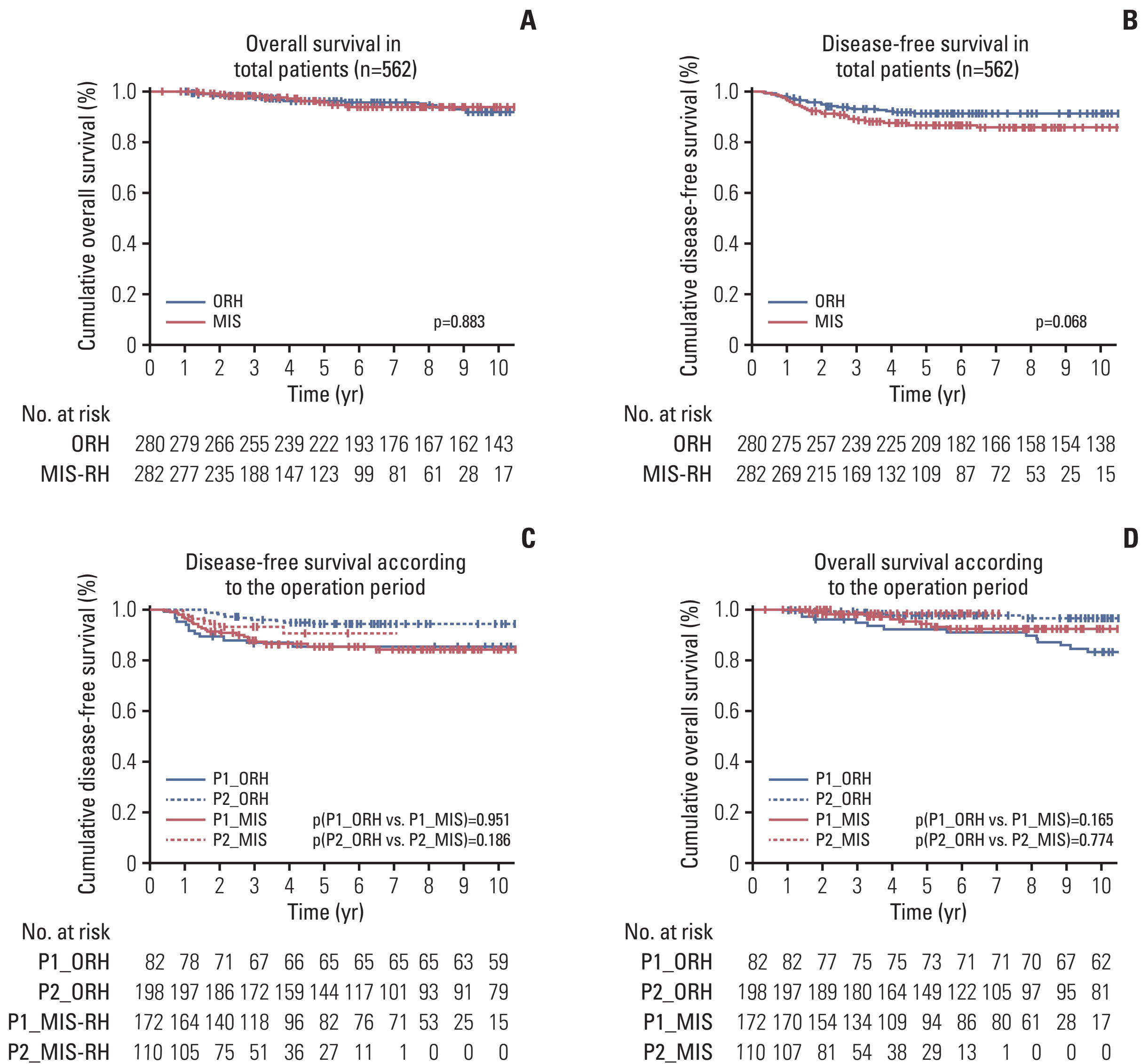
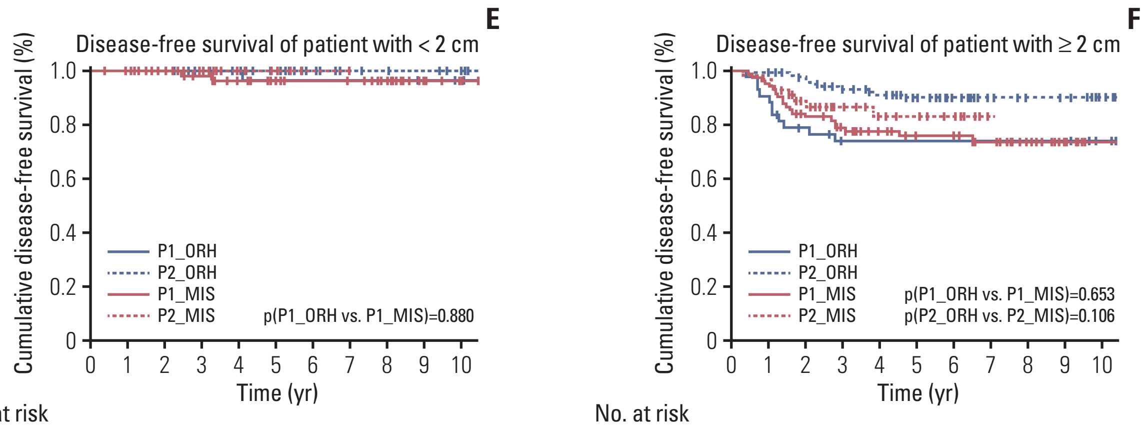


Fig. 1. Kaplan-Meier estimates of overall survival (A, D) and disease-free survival (B, C, E, F) for cervical cancer patients treated with open radical hysterectomy (ORH) and minimally invasive surgery-radical hysterectomy (MIS-RH). (A) The 5-year overall survival of open and minimally invasive groups were 96.1% (269/280) and 97.2% (274/282), respectively, p=0.944. (B) The 5-year disease-free survival of open and minimally invasive groups were 91.8% (257/280) and 89.0% (251/282), respectively, p=0.098. (C, D) P1 phase presented significantly worse survival rates than P2 phase in the open group (disease-free survival: 85.4% vs. 94.4%, p=0.011; overall survival: 84.1% vs. 97.5%, p=0.001). However, the minimally invasive group did not show statistically significant difference in survival rates of P1 and P2 phase (disease-free survival: 86.0% vs. 92.7%, p=0.233; overall survival: 94.8% vs. 99.1%, p=0.194). Also, there was no significant difference in survival rates between the two groups either in the P1 phase or P2. *(Continued to the next page)*

radical hysterectomy and pelvic lymphadenectomy. Colpotomy was done intracorporeally in all patients. Para-aortic lymphadenectomy or bilateral salpingo-oophorectomy was performed on the basis of patients' individual factors. The tumor size was sum of the greatest measured diameter of cone biopsy and the gross size measured via magnetic resonance imaging after biopsy. Tumor size by magnetic resonance imaging was determined by the greater length. Other histologic types included small cell carcinoma, neuroendocrine carcinoma, and adenosarcoma. Recurrence of cancer was confirmed by clinical findings, radiological examinations, and pathology reports in both groups. The two groups have the same frequency of surveillance. The survival period was measured from the date of surgery to the recurrence of



No. at risk (E)	0	1	2	3	4	5	6	7	8	9	10
P1_ORH	30	30	30	30	30	29	29	29	29	27	26
P2_ORH	56	56	56	54	51	47	39	35	33	32	30
P1_MIS	70	69	60	51	43	38	35	34	26	12	9
P2_MIS	43	41	30	21	13	9	3	0	0	0	0

No. at risk (F)	0	1	2	3	4	5	6	7	8	9	10
P1_ORH	43	39	32	28	28	28	28	28	28	28	25
P2_ORH	123	122	112	101	92	81	62	51	45	44	35
P1_MIS	84	79	65	57	47	38	37	33	24	12	6
P2_MIS	58	55	39	28	21	16	7	1	0	0	0

Fig. 1. *(Continued from the previous page)* (E) In the subgroup of patients with tumors < 2 cm, operation period or mode had little effect on disease-free survival. (F) In the subgroup of patient with ≥ 2 cm, P1 phase presented significantly worse disease-free survival than P2 phase in the open group (74.4% [32/43] vs. 91.1% [112/123], p=0.003). The minimally invasive group showed the same tendency but it was not significant (77.4% [65/84] vs. 86.2% [50/58], p=0.193).

the disease, the last follow-up date, or death.

2. Statistical analysis

Chi-square test was used to compare categorical variables. Mann-Whitney test was used for nonparametric data. Survival curves were generated using the Kaplan-Meier method and analyzed with log-rank test. Univariate and multivariate analyses were performed using Cox proportional hazards model. Hazard ratios (HR) greater than 1.0 implied increased likelihood of recurrence or death. The learning curve was evaluated by 5-year recurrence number using the cumulative sum method [16]. The cumulative sum method of recurrence number for every 10th procedure is defined as $\Sigma(X_t–X_0)$, (t=10, 20, 30…), where X_0 was the mean recurrence number for all the cases, X_t was value for each 10 cases recurrence number. The number of recurrences per 10 cases shown in the chart was the average number of recurrences per 10 cases by all surgeons.

All statistical analyses were performed using SPSS Statistics ver. 25 (IBM Corp., Armonk, NY). Two-sided significant p-value less than 0.05 was regarded as statistically significant.

Results

1. Characteristics and surgical outcomes

Of the 562 selected patients, traditional open surgeries (n=280) were performed from January 2002 to June 2018, and minimal invasive surgeries (laparoscopic radical hysterectomy, n=127 and robotic radical hysterectomy, n=155) from January 2006 to June 2018. The proportions of type III were 254 (90.7%) and 263 (93.3%) in the open and minimally invasive groups. Patient characteristics of age, body mass index, tumor size, lympho-vascular space invasion, resection margin involvement, and histologic type were not significantly different between the open and minimal invasive radical hysterectomy groups (Table 1). Deep cervical stromal invasion, higher FIGO stage, lymph node metastasis, and postoperative adjuvant treatment were more frequent in the open group.

2. Total survival outcomes of open and minimally invasive radical hysterectomy

In total, we observed 18 deaths and 23 recurrences over a median follow-up of 10.1 years in the open group, and 10 deaths and 32 recurrences over a median follow-up of 4.2 years in the minimally invasive group. With regard to overall survival, statistically significant difference was not observed (Fig. 1A). The 5-year overall survival was 96.1% (269/280) in open group and 97.2% (274/282) in minimally invasive group (p=0.944). With regard to disease-free survival, there was no significant difference between the two groups (Fig. 1B). The 5-year disease-free survival rates were 91.8% (257/280) in the open group and 89.0% (251/282) in the minimally invasive group (p=0.098). The cumulative sum learning curve

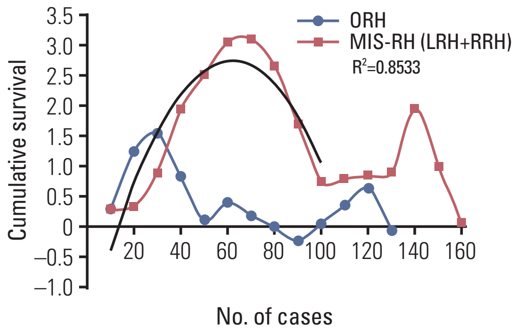


Fig. 2. Learning curve analysis with regard to 5-year recurrence number. Cumulative sum for 5-year recurrence number of every 10 cases was plotted. The 5-year recurrence number decreased after 30 cases in open group, and after 60 cases in the minimally invasive group. LRH, laparoscopic radical hysterectomy; MIS-RH, minimally invasive surgery-radical hysterectomy; ORH, open radical hysterectomy; RRH, robotically assisted radical hysterectomy.

showed that 5-year recurrence numbers were significantly decreased at a turning point of 30 cases in the open group, and 60 cases in the minimally invasive group (Fig. 2). Open and minimally invasive groups were further divided into two cohorts by surgeon proficiency. (P1, 0-30 cases of open group or 0-60 cases of minimally invasive groups; P2, > 30 cases of open group or > 60 cases of minimally invasive group). Cox proportional univariate analysis of 5-year disease-free survival showed significant differences in terms of invasion depth, initial tumor size, histologic type, lympho-vascular space invasion, FIGO stage, learning curve, and postoperative adjuvant treatment (S2 Table). In the multivariate analysis of 5-year disease-free survival, the P2 group had lower risk of recurrence than P1 group after adjusting for invasion depth, tumor size, histologic type, lympho-vascular space invasion, and operation mode (HR, 0.392; 95% confidence interval [CI], 0.210 to 0.734; p=0.003) (Table 2). Initial tumor size also had a significant effect on disease-free survival in multivariate analysis (HR, 15.242; 95% CI, 4.644 to 50.027; p < 0.001). Cox proportional univariate analysis for overall survival was showed in S3 Table.

3. Survival outcomes and surgeon proficiency

Except for invasion depth and postoperative adjuvant treatment, there was no significant difference in clinical characteristics between the two groups in P1 and P2 phases (S4 Table). Median follow-up duration was 8.1 and 5.6 years in P1 and P2, respectively.

The survival rates of P1 were significantly lower than those of P2 phase in open group (disease-free survival, 85.4%

Table 2. Multivariate Cox regression analysis for 5-year disease-free survival

Variable	Total (n= 562)	HR (95% CI)	p-value
Invasion depth (cm)			
≤ 1	427	1 (reference)	0.948
> 1	135	0.981 (0.549-1.753)	
Tumor size (cm)			
< 2	249	1 (reference)	
≥ 2	313	15.242 (4.644-50.027)	< 0.001
Histologic type			
Squamous cell	368	1 (reference)	
Adenocarcinoma	158	1.605 (0.844-3.053)	0.149
Adenosquamous	24	3.758 (1.415-9.983)	0.008
Other type	12	8.158 (3.233-20.584)	< 0.001
Lympho-vascular space invasion			
Negative	351	1 (reference)	0.251
Positive	211	1.404 (0.786-2.506)	
Operation mode			
Open surgery	280	1 (reference)	0.405
Minimally invasive surgery	282	1.292 (0.708-2.358)	
Learning curve			
P1[a)]	234	1 (reference)	0.003
P2[b)]	328	0.392 (0.210-0.734)	

CI, confidence interval; HR, hazard ratio. [a)]P1 (learning period), 0-30 cases of open radical hysterectomy (ORH) or 0-60 cases of minimally invasive radical hysterectomy (MIS-RH), [b)]P2 (skilled period), > 30 cases of ORH or > 60 cases of MIS-RH.

Table 3. 5-Year disease-free survival rates of two groups according to the tumor size and operation period

Tumor size (cm)	P1[a)]			P2[b)]			Total		
	Open surgery	Minimally invasive surgery	p-value	Open surgery	Minimally invasive surgery	p-value	Open surgery	Minimally invasive surgery	p-value
< 2	29/30 (96.7)	68/70 (97.1)	0.880	56/56 (100)	43/43 (100)	-	85/86 (98.8)	111/113 (98.2)	0.461
≥ 2	32/43 (74.4)	65/84 (77.4)	0.652	112/123 (91.1)	50/58 (86.2)	0.106	144/166 (86.7)	115/142 (81.0)	0.089
Total	61/73 (83.6)	133/154 (86.4)	0.674	168/179 (93.9)	93/101 (92.1)	0.202	229/252 (90.9)	226/255 (88.6)	0.177

Values are presented as number (%). [a)]P1 (learning period), 0-30 cases of open radical hysterectomy (ORH) or 0-60 cases of minimally invasive radical hysterectomy (MIS-RH), [b)]P2 (skilled period), > 30 cases of ORH or > 60 cases of MIS-RH.

in P1 vs. 94.4% in P2, p=0.011; overall survival, 84.1% in P1 vs. 97.5% in P2, p=0.001) (Fig. 1C and D). There was no statistical significance in minimally invasive group (disease-free survival: 86.0% vs. 92.7%, p=0.233; overall survival: 94.8% vs. 99.1%, p=0.194). The disease-free survival rates of open and minimally invasive group were comparable both in P1 and P2 (P1, 85.4% vs. 86.0%; P2, 94.4% vs. 92.7%). Overall survival of minimally invasive group (94.8%) was higher than that of open group (84.1%) in P1 but it was not statistically significant. Overall survival rates of the open and minimally invasive group were comparable in P2 (97.5% vs. 99.1%).

The most common recurrence site in the P1 phase was the pelvic cavity in open group and the vagina in minimally invasive group. However, recurrence rates of these sites dramatically declined in the P2 phase (S5 Fig.).

4. Survival outcomes by tumor size

On the subgroup analysis by tumor size, we excluded IA stage (n=55) patients. When comparing survival rates by tumor size, both in the two groups, the 5-year disease-free survival rates decreased when tumor size increased (Table 3). Patients with small tumor size (< 2 cm) did not show any difference in disease-free survival based on operation mode or phase (Fig. 1E). However, in patients with a tumor size ≥ 2 cm, P1 phase presented significantly worse disease-free survival than P2 phase in the open group (74.4% vs. 91.1%, p=0.003). There was no significant difference in the minimally invasive group (77.4% vs. 86.2%, p=0.193) (Fig. 1F).

The survival rate of minimally invasive group was slightly better than open group with tumor size ≥ 2 cm in P1 (77.4% vs. 74.4%, p=0.652). Minimally invasive group presented lower survival rates than open group when tumor size ≥ 2 cm in P2 (86.2% vs. 91.1%, p=0.106). However, if the patient underwent preoperative conization the survival rates of two groups were comparable when tumor size ≥ 2 cm in P2 (94.7% vs. 94.6%) (S6 Table). Besides, we found that patients that underwent preoperative conization presented significantly better disease-free survival than patients without conization in the P1 minimally invasive group (89.2% vs. 68.1%, p=0.027) (S6 and S7 Tables).

Discussion

Minimally invasive techniques, including robotic surgery, developed rapidly because of their intraoperative and postoperative advantages with comparable survival outcomes [14,17,18]. As research advances, the conclusion that minimally invasive surgery has a better survival outcome than open surgery has not changed [19]; however, in 2017, conflicting survival data of minimally invasive radical hysterectomy began to be reported [11,20]. A number of recent meta-analysis studies suggested that there were no significant differences between open and minimally invasive radical hysterectomy [21-24]. However, in the study by Ramirez et al., the three-year survival rates of the minimally invasive radical hysterectomy groups are much lower than open radical hysterectomy group.

Our results showed there was no significant difference in disease-free survival between the two groups. However, when we divided consecutive cases into two groups (initial cases and late cases), we noticed that disease-free survival of the minimally invasive group in the late case phase was significantly better than in initial cases. This result prompted us to draw the learning curve of disease-free survival in order to find out whether there were differences in survival outcomes before or after reaching learning curve and standardization of the technique. Our previous study [14] on learning curve analysis showed that the learning curve for proficiency and efficiency in robot-assisted radical hysterectomy was 28 cases. However, the proficiency of surgery in that study was mainly defined as short docking or console time, less blood loss, and fewer postoperative complication rates. To date, there is scarce research on learning curve analysis based on actual survival. Chong et al. [25] compared the learning period of robotic (consecutive 65 cases) and skilled period of laparoscopic radical hysterectomy for early-stage cervical cancer. However, the number of learning period cases was not determined according to the learning curve but was randomly included in the consecutive 65 cases. Calculating the learning curve of radical hysterectomy and analyzing survival outcomes according to the learning curve was the primary strength of our study.

Our results indicated that 5-year disease-free survival was better when the surgeon reached the learning curve. However, minimally invasive group need more cases than open cases (30 cases vs. 60 cases) to reach learning curve. The need for more cases to reach the learning curve means more recurrence rates during the initial period of time. Several factors were discussed for the higher recurrence rate of cervical cancer [26-28]. The most commonly mentioned factor was the spread of cancer during intracorporeal colpotomy. However, all surgeons in our study performed intracorporeal colpotomy during minimally invasive surgery and we did not compare the survival outcomes between vaginal colpotomy and intracorporeal colpotomy. Normally, cervical tumor size was considered highly associated with vaginal vault recurrence. In our study, the vaginal vault was the most common recurrence site in the minimally invasive group. We also identified that 5-year disease-free survival rates were higher in the smaller-sized tumor group both in open and minimally invasive surgery.

Requiring more cases to reach learning curve may cause unexperienced surgeons to hesitate to perform minimally invasive surgery on patients during this period. However, the minimally invasive group showed a comparable disease-free survival rate to that of the open group in the learning period, even if the tumor exceeded 2 cm. This means that we should focus not on the mode of operation, but on reducing the recurrence rate during the learning period. For example, as our result confirmed, preoperative conization may be an effective way to reduce recurrence rate in minimally invasive radical hysterectomy.

Our study has several limitations. First of all, as we mentioned previously, the type of colpotomy may be associated with postoperative disease-free survival. The effect of the uterine manipulator on the disease-free survival between vaginal and intracorporeal colpotomy should be analyzed. Secondly, the 5-year follow-up period was not complete in all patients. Future work with updated data is required in order to obtain more accurate results. Finally, the effectiveness of preoperative conization or should be fully and systematically analyzed.

In summary, the 5-year disease-free survival rate of early-stage cervical cancer patients improved after performing 30 and 60 surgeries for open radical hysterectomy and minimally invasive radical hysterectomy, respectively. The survival rates in patients with tumors smaller than 2 cm were not affected by the surgeon's proficiency both in open and minimally invasive group. Survival outcomes of two groups with tumor size ≥ 2 cm were similar during the learning period, but were both better during skilled period. Special attention needs to be paid to decrease the number of surgeries required to reach learning curve, especially in patients with a relatively large tumor size.

Electronic Supplementary Material

Supplementary materials are available at Cancer Research and Treatment website (https://www.e-crt.org).

Ethical Statement

This study was approved by the Yonsei University Severance Hospital Institutional Review Board (number: 4-2018-1001). The informed consent was waived.

Author Contributions

Conceived and designed the analysis: Li LY, Park SH, Kim SW.
Collected the data: Li LY, Wen LY, Park SH, Kim SW.
Contributed data or analysis tools: Li LY, Lee JY, Nam EJ, Kim S, Kim YT, Kim SW.
Performed the analysis: Li LY, Wen LY, Kim SW.
Wrote the paper: Li LY, Kim SW.

Conflicts of Interest

Conflicts of interest relevant to this article was not reported.

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