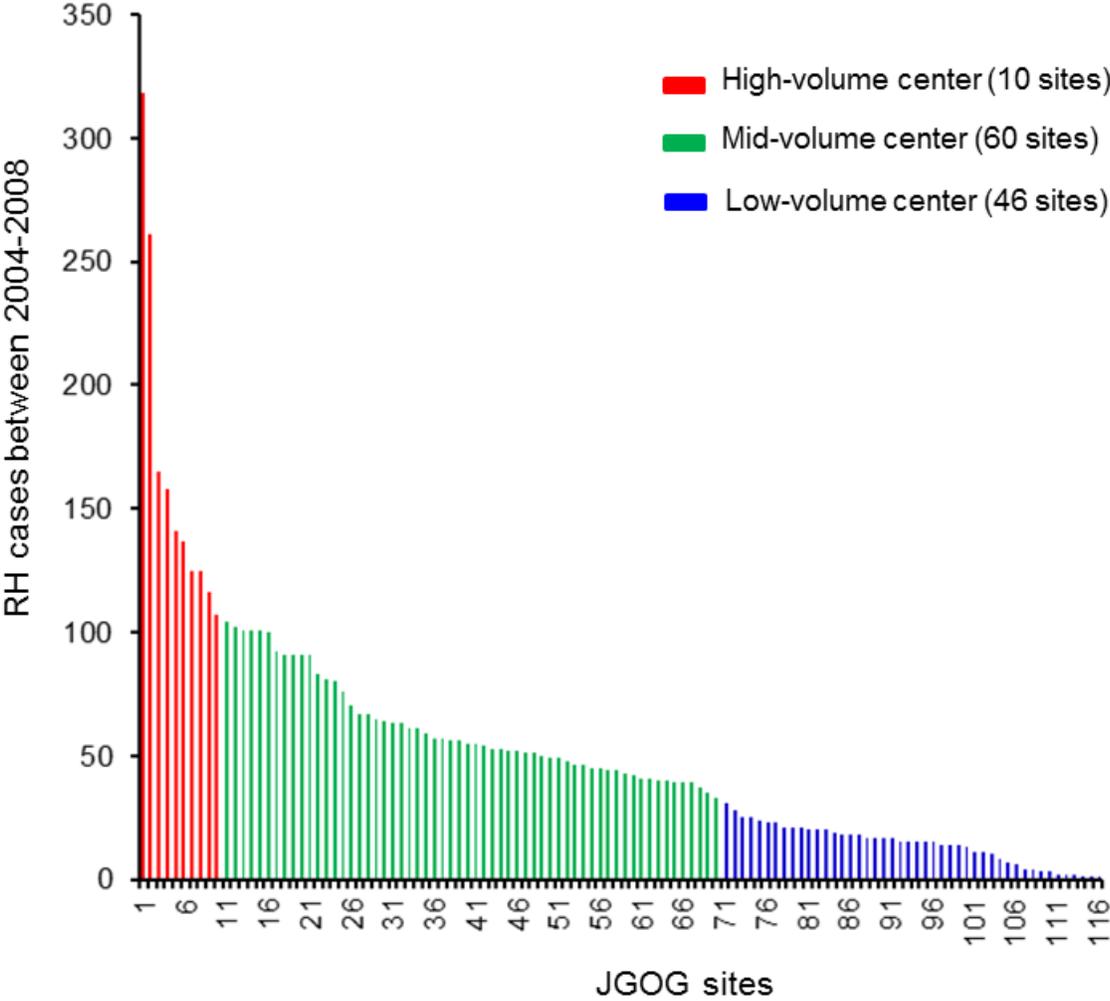


Appendix 1. Histogram of surgical volume for 116 JGOG sites. Consecutive cases of radical hysterectomy performed for clinical stage IB1-IIIB cervical cancer between 2004 and 2008 are shown based on number (large to small). The median number of radical hysterectomy over five-year study duration was 44 (interquartile range, 17-65). RH, radical hysterectomy; JGOG, Japanese Gynecologic Oncology Group.



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Appendix 2. Adjusting Model 1 (Unadjusted Baseline)

Characteristic	Disease-free survival		Overall survival		Local-recurrence		Distant-recurrence	
	HR (95%CI)	P-value	HR (95%CI)	P-value	HR (95%CI)	P-value	HR (95%CI)	P-value
All cases (pre-matching)								
Mid-volume	1		1		1		1	
High-volume	0.743 (0.642-0.860)	<0.001	0.844 (0.707-1.008)	0.061	0.667 (0.548-0.813)	<0.001	0.915 (0.757-1.106)	0.359
Low-volume	1.209 (1.011-1.446)	0.038	0.995 (0.780-1.269)	0.968	1.016 (0.794-1.298)	0.902	1.157 (0.901-1.488)	0.252
All cases (post-matching)								
mid-/low-volume	1		1		1		1	
High-volume	0.681 (0.577-0.803)	<0.001	0.773 (0.637-0.937)	0.009	0.635 (0.509-0.793)	<0.001	0.795 (0.642-0.986)	0.037
Stage IB1 disease*								
Mid-volume	1		1		1		1	
High-volume	0.567 (0.355-0.906)	0.018	0.503 (0.241-1.051)	0.068	0.495 (0.290-0.846)	0.010	0.705 (0.312-1.592)	0.401
Low-volume	0.944 (0.524-1.703)	0.849	0.330 (0.079-1.374)	0.128	0.941 (0.496-1.785)	0.851	0.513 (0.120-2.190)	0.368
Stage IIB disease								
Mid-volume	1		1		1		1	
High-volume	0.764 (0.598-0.977)	0.032	0.928 (0.706-1.221)	0.594	0.761 (0.550-1.053)	0.099	0.902 (0.659-1.236)	0.522
Low-volume	1.008 (0.743-1.369)	0.958	0.943 (0.649-1.370)	0.759	0.775 (0.497-1.210)	0.262	1.016 (0.675-1.529)	0.940
Node-positive case								
Mid-volume	1		1		1		1	
High-volume	0.778 (0.637-0.951)	0.014	0.898 (0.718-1.123)	0.346	0.694 (0.521-0.926)	0.013	0.930 (0.732-1.182)	0.553
Low-volume	1.020 (0.787-1.322)	0.881	1.005 (0.742-1.359)	0.976	0.971 (0.677-1.394)	0.875	0.957 (0.685-1.335)	0.794

Association for surgical volume and survival outcome was adjusted for preoperative factors: age (continuous), year of diagnosis (2004, 2005, 2006, 2007, and 2008), and histology (squamous *versus* non-squamous). Cox proportional hazard regression models were used for analysis. Significant *P*-values are emboldened. *Clinical stage IB1 disease without preoperative / postoperative chemotherapy / radiotherapy. Abbreviations: HR, hazard ratio; and CI, confidence interval.

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Appendix 3. Adjusting Model 2 (Pretreatment Factors)

Characteristic	Disease-free survival		Overall survival		Local-recurrence		Distant-recurrence	
	HR (95%CI)	P-value	HR (95%CI)	P-value	HR (95%CI)	P-value	HR (95%CI)	P-value
All cases (pre-matching)								
Mid-volume	1		1		1		1	
High-volume	0.752 (0.649-0.871)	<0.001	0.862 (0.727-1.022)	0.086	0.677 (0.555-0.825)	<0.001	0.926 (0.765-1.120)	0.426
Low-volume	1.225 (1.024-1.466)	0.027	0.986 (0.778-1.251)	0.908	1.014 (0.792-1.298)	0.912	1.184 (0.921-1.522)	0.187
All cases (post-matching)								
mid-/low-volume	1		1		1		1	
High-volume	0.679 (0.575-0.801)	<0.001	0.771 (0.636-0.935)	0.008	0.633 (0.506-0.790)	<0.001	0.797 (0.643-0.988)	0.038
Stage IB1 disease*								
Mid-volume	1		1		1		1	
High-volume	0.588 (0.367-0.940)	0.027	0.482 (0.230-1.011)	0.054	0.509 (0.297-0.871)	0.014	0.729 (0.322-1.653)	0.449
Low-volume	0.932 (0.515-1.686)	0.816	0.357 (0.085-1.492)	0.158	0.934 (0.491-1.777)	0.835	0.530 (0.124-2.269)	0.392
Stage IIB disease								
Mid-volume	1		1		1		1	
High-volume	0.803 (0.627-1.028)	0.081	0.971 (0.732-1.286)	0.835	0.798 (0.576-1.105)	0.174	0.945 (0.688-1.296)	0.724
Low-volume	1.068 (0.785-1.453)	0.676	1.021 (0.697-1.496)	0.913	0.825 (0.528-1.290)	0.400	1.027 (0.681-1.549)	0.899
Node-positive case								
Mid-volume	1		1		1		1	
High-volume	0.790 (0.646-0.966)	0.021	0.926 (0.738-1.162)	0.507	0.713 (0.534-0.951)	0.021	0.934 (0.734-1.188)	0.577
Low-volume	1.038 (0.800-1.347)	0.776	1.056 (0.777-1.435)	0.728	0.969 (0.674-1.392)	0.864	0.964 (0.690-1.346)	0.829

Association for surgical volume and survival outcome was adjusted for pretreatment factors: age (continuous), year of diagnosis (2004, 2005, 2006, 2007, and 2008), and histology (squamous *versus* non-squamous). Cox proportional hazard regression models were used for analysis. Significant *P*-values are emboldened. *Clinical stage IB1 disease without preoperative / postoperative chemotherapy / radiotherapy. Abbreviations: HR, hazard ratio; and CI, confidence interval.

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Appendix 4. Adjusting Model 3 (Pretreatment Factors and Surgical-Pathological Results)

Characteristic	Disease-free survival		Overall survival		Local-recurrence		Distant-recurrence	
	HR (95%CI)	<i>P</i> -value	HR (95%CI)	<i>P</i> -value	HR (95%CI)	<i>P</i> -value	HR (95%CI)	<i>P</i> -value
All cases (pre-matching)								
Mid-volume	1		1		1		1	
High-volume	0.685 (0.583-0.804)	<0.001	0.717 (0.587-0.875)	0.001	0.624 (0.503-0.774)	<0.001	0.820 (0.665-1.012)	0.064
Low-volume	1.136 (0.937-1.377)	0.195	0.961 (0.738-1.250)	0.767	1.004 (0.773-1.303)	0.978	0.928 (0.700-1.230)	0.603
All cases (post-matching)								
mid-/low-volume	1		1		1		1	
High-volume	0.683 (0.569-0.820)	<0.001	0.733 (0.584-0.920)	0.008	0.634 (0.497-0.808)	<0.001	0.784 (0.817-0.998)	0.048
Stage IB1 disease*								
Mid-volume	1		1		1		1	
High-volume	0.496 (0.295-0.833)	0.008	0.351 (0.151-0.815)	0.015	0.445 (0.246-0.806)	0.008	0.538 (0.222-1.308)	0.171
Low-volume	1.009 (0.545-1.866)	0.977	0.343 (0.081-1.458)	0.147	0.989 (0.506-1.934)	0.974	0.540 (0.125-2.339)	0.410
Stage IIB disease								
Mid-volume	1		1		1		1	
High-volume	0.734 (0.556-0.970)	0.030	0.824 (0.599-1.134)	0.235	0.657 (0.455-0.947)	0.024	0.880 (0.613-1.263)	0.487
Low-volume	0.967 (0.691-1.353)	0.844	0.981 (0.653-1.474)	0.926	0.780 (0.485-1.254)	0.305	0.883 (0.552-1.410)	0.602
Node-positive case								
Mid-volume	1		1		1		1	
High-volume	0.738 (0.592-0.920)	0.007	0.762 (0.591-0.984)	0.037	0.630 (0.459-0.864)	0.004	0.890 (0.682-1.162)	0.391
Low-volume	0.928 (0.703-1.223)	0.595	0.966 (0.698-1.337)	0.835	0.883 (0.800-1.299)	0.528	0.822 (0.569-1.187)	0.296

Association for surgical volume and survival outcome was adjusted for pretreatment factors (Table S1) and surgical pathological factors: pelvic lymph node metastasis (yes *versus* no), para-aortic lymph node metastasis (yes, no, or not examined), parametrial involvement (yes *versus* no), deep stromal invasion (yes *versus* no), LVSI (yes *versus* no), tumor size (>4 *versus* ≤4 cm), uterine corpus invasion (yes *versus* no), ovarian metastasis (yes *versus* no), and malignant peritoneal cytology (yes, no, or not examined). Cox proportional hazard regression models were used for analysis. Significant *P*-values are emboldened. *Clinical stage IB1 disease without preoperative / postoperative chemotherapy / radiotherapy. Abbreviations: HR, hazard ration; and CI, confidence interval.

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Appendix 5. Association of Surgical Volume and Survival in Cervical Cancer (Adjusting Model 3).

Characteristic	Disease-free survival		Overall survival		Local-recurrence		Distant-recurrence	
	HR (95%CI)	P-value	HR (95%CI)	P-value	HR (95%CI)	P-value	HR (95%CI)	P-value
All cases (pre-matching)								
Mid-volume	1		1		1		1	
High-volume	0.704 (0.590-0.840)	<0.001	0.744 (0.603-0.919)	0.006	0.632 (0.500-0.799)	<0.001	0.857 (0.678-1.082)	0.194
Low-volume	1.137 (0.928-1.392)	0.215	0.879 (0.667-1.158)	0.358	0.969 (0.737-1.275)	0.823	0.966 (0.717-1.302)	0.820

Association for surgical volume and survival outcome was adjusted for pretreatment factors, surgical-pathological results, and treatment types (adjusting model 3). Pretreatment factors: age (continuous), year of diagnosis (2004, 2005, 2006, 2007, and 2008), and histology (squamous *versus* non-squamous). Surgical-pathological factors: pelvic lymph node metastasis (yes *versus* no), para-aortic lymph node metastasis (yes, no, or not examined), parametrial involvement (yes *versus* no), deep stromal invasion (yes *versus* no), LVSI (yes *versus* no), tumor size (>4 *versus* ≤4 cm), uterine corpus invasion (yes *versus* no), ovarian metastasis (yes *versus* no), and malignant peritoneal cytology (yes, no, or not examined). Treatment types: number of sampled pelvic lymph nodes (continuous), neoadjuvant chemotherapy (yes *versus* no), and adjuvant therapy (radiation-based, chemotherapy-based, or none). Cox proportional hazard regression models were used for analysis. Proportional hazard assumption was tested and showed no interaction with time. Significant *P*-values are emboldened. *Clinical stage IB1 disease without preoperative / postoperative chemotherapy / radiotherapy. Abbreviations: HR, hazard ratio; and CI, confidence interval.

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Appendix 6. Association of Surgical Volume and Survival in Cervical Cancer (Adjusting Model 3).

Characteristic	Disease-free survival		Overall survival		Local-recurrence		Distant-recurrence	
	HR (95%CI)	P-value	HR (95%CI)	P-value	HR (95%CI)	P-value	HR (95%CI)	P-value
All cases (pre-matching)								
Mid-volume	1		1		1		1	
High-volume	0.730 (0.623-0.857)	<0.001	0.726 (0.596-0.885)	0.002	0.643 (0.518-0.797)	<0.001	0.850 (0.684-1.055)	0.141
Low-volume	1.084 (0.893-1.316)	0.415	0.858 (0.658-1.118)	0.256	0.972 (0.749-1.260)	0.828	0.899 (0.673-1.201)	0.471

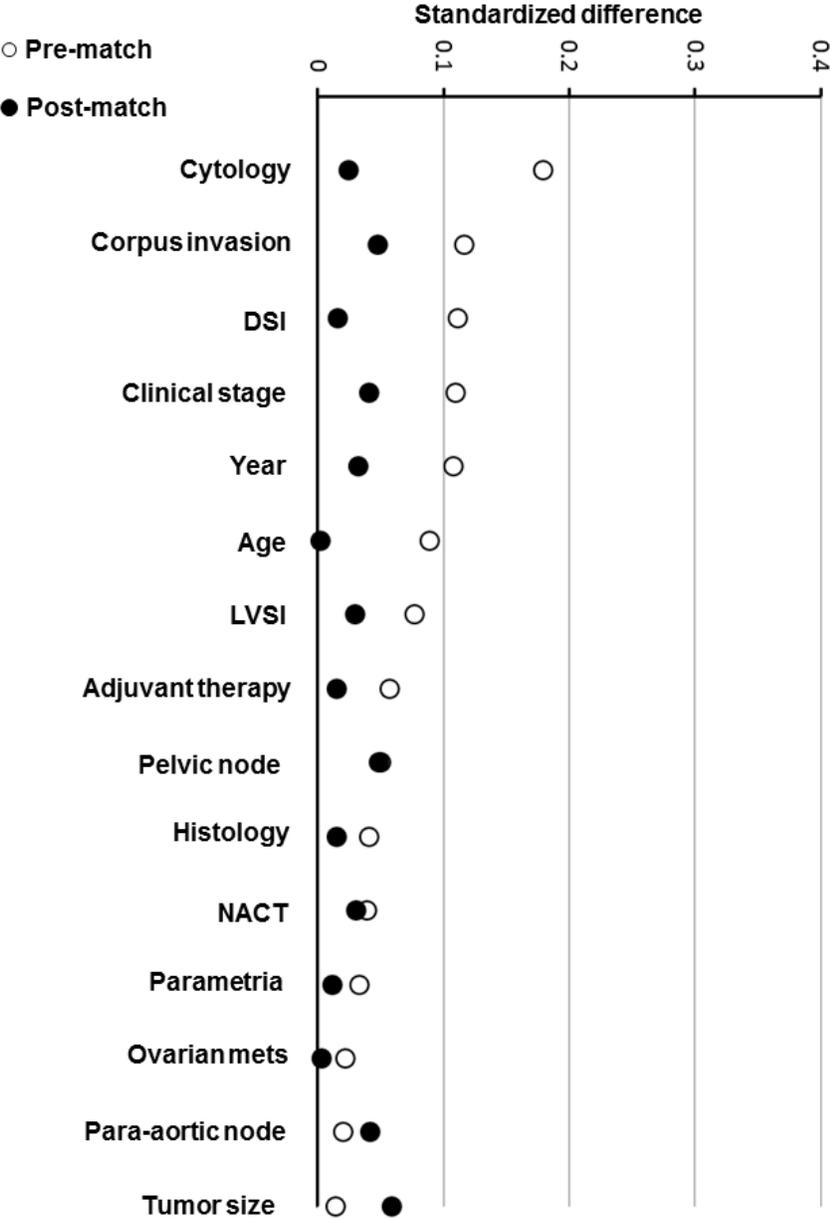
Treatment initiating date either with surgery or neoadjuvant therapy was used. Association for surgical volume and survival outcome was adjusted for pretreatment factors, surgical-pathological results, and treatment types (adjusting model 3). Pretreatment factors: age (continuous), year of diagnosis (2004, 2005, 2006, 2007, and 2008), and histology (squamous *versus* non-squamous). Surgical-pathological factors: pelvic lymph node metastasis (yes *versus* no), para-aortic lymph node metastasis (yes, no, or not examined), parametrial involvement (yes *versus* no), deep stromal invasion (yes *versus* no), LVSI (yes *versus* no), tumor size (>4 *versus* ≤4 cm), uterine corpus invasion (yes *versus* no), ovarian metastasis (yes *versus* no), and malignant peritoneal cytology (yes, no, or not examined). Treatment types: number of sampled pelvic lymph nodes (continuous), neoadjuvant chemotherapy (yes *versus* no), and adjuvant therapy (radiation-based, chemotherapy-based, or none). Cox proportional hazard regression models were used for analysis. Proportional hazard assumption was tested and showed no interaction with time. Significant *P*-values are emboldened. *Clinical stage IB1 disease without preoperative / postoperative chemotherapy / radiotherapy. Abbreviations: HR, hazard ration; and CI, confidence interval.

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Appendix 7. Standardized difference for propensity score matching. Standardized difference before and after propensity score matching is shown. The value of ≤ 0.10 indicates good balance between the two groups. DSI, deep stromal invasion; LVSI, lymphovascular space invasion; NACT, neoadjuvant chemotherapy; and mets, metastasis.



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Appendix 8. Interaction of Surgical Volume and Adjuvant Therapy for Survival

Characteristic	Disease-free survival		Overall survival		Local-recurrence		Distant-recurrence	
	HR (95%CI)	<i>P</i> -value	HR (95%CI)	<i>P</i> -value	HR (95%CI)	<i>P</i> -value	HR (95%CI)	<i>P</i> -value
High-volume								
Radiotherapy	1		1		1		1	
Chemotherapy	0.678 (0.395-1.165)	0.160	0.947 (0.541-1.660)	0.850	1.099 (0.516-2.340)	0.807	0.564 (0.295-1.076)	0.082
Mid- / Low-volume								
Radiotherapy	1		1		1		1	
Chemotherapy	1.131 (0.853-1.500)	0.391	1.059 (0.762-1.472)	0.734	1.664 (1.140-2.430)	0.008	0.662 (0.447-0.978)	0.038

Examined women with pelvic lymph node positive who received radiotherapy (whole pelvic alone or concurrent chemo-radiotherapy) or systemic chemotherapy alone. Women who received neoadjuvant therapy were excluded. Cox proportional hazard regression model for *P*-values. Association of surgical volume and adjuvant therapy type was adjusted for histology, parametrial involvement, and lymph node ratio. Significant *P*-values are emboldened. Abbreviations: HR, hazard ratio; CI, confidence interval.

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Appendix 9. Association of Surgical Volume and Local-Recurrence Risk (Stage IB1 Disease, n=1,700)

RH over 5 years	Number	HR (95%CI)	
		versus 20-29 cases	P-value
<10 cases	237	0.915 (0.474-1.763)	0.790
10-19 cases	441	0.651 (0.356-1.194)	0.165
20-29 cases	313	1	
30-49 cases	360	0.875 (0.485-1.581)	0.875
≥50 cases	349	0.460 (0.227-0.929)	0.030

1,700 women with clinical stage IB1 cervical cancer who underwent primary RH without neoadjuvant therapy or postoperative therapy were examined. Surgical volume for RH per institution during the study period (5 years) was arbitrary grouped every 10-20 cases. Association for surgical volume and cumulative local-recurrence risk was examined with a Cox proportional hazard regression model. Significant P-values are emboldened. Abbreviations: RH, radical hysterectomy; HR, hazard ration; and CI, confidence interval.

Appendix 10. Proportion of Institutions Crossed Over the Groups

Intragroup crossover	Low-volume	Mid-volume	High-volume
No	28 (61%)	22 (36.7%)	4 (40%)
Yes	18 (39%)	38 (63.3%)	6 (60%)
Total	46 sites	60 sites	10 sites

Each institution grouped as low-volume group, mid-volume group, and high-volume group based on the 5-year surgical volume was assessed surgical volume in each calendar year for five years during study window of 2004-2008. Based on the cutoff surgical cases over 5-year period (Figure 1), we arbitrary used the annual cutoff of surgical volume as: low-volume (≤ 6 surgeries per year), mid-volume (7-20 surgeries per year), and high-volume (≥ 21 surgeries per year). In intergroup variability was assessed in each given calendar year. Institutions remained as the assigned group based on the 5-year surgical volume definition was allocated as no intergroup crossover whereas institutions changed the case number to different category was allocated as intergroup crossover.