Original Research

Association of Hospital Surgical Volume With Survival in Early-Stage Cervical Cancer Treated With Radical Hysterectomy

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OBJECTIVE: To evaluate the association of number of radical hysterectomies performed per year in each center with disease-free survival and overall survival.

METHODS: We conducted an international, multicenter, retrospective study of patients previously included in the Surveillance in Cervical Cancer collaborative studies. Individuals with International Federation of Gynecology and Obstetrics (FIGO) 2009 stage IB1–IIA1 cervical cancer who underwent radical hysterectomy and had negative lymph nodes at final histology were included. Patients were treated at referral centers for gynecologic oncology according to updated national and international guidelines. Optimal cutoffs for surgical volume were identified using an unadjusted Cox proportional hazard model, with disease-free survival as the outcome and defined as the value that minimizes the *P*-value of the split in groups in terms of disease-free survival. Propensity score match-

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ing was used to create statistically similar cohorts at baseline.

RESULTS: A total of 2,157 patients were initially included. The two most significant cutoffs for surgical volume were identified at seven and 17 surgical procedures, dividing the entire cohort into low-volume, middle-volume, and high-volume centers. After propensity score matching, 1,238 patients were analyzed—619 (50.0%) in the high-volume group, 523 (42.2%) in the middle-volume group, and 96 (7.8%) in the low-volume group. Patients who underwent surgery in higher-volume institutions had progressively better 5-year disease-free survival than those who underwent surgery in lower-volume centers (92.3% vs 88.9% vs 83.8%, P=.029). No difference was noted in 5-year overall survival (95.9% vs 97.2% vs 95.2%, P=.70). Cox multivariable regression analysis showed that FIGO stage greater than IB1, presence of lymphovascular space invasion, grade greater than 1, tumor diameter greater than 20 mm, minimally invasive surgical approach, nonsquamous cell carcinoma histology, and lower-volume centers represented independent risk factors for recurrence.

CONCLUSION: Surgical volume of centers represented an independent prognostic factor affecting disease-free survival. Increasing number of radical hysterectomies performed in each center every year was associated with improved disease-free survival.

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Despite the introduction and implementation of screening and vaccination programs, cervical cancer remains a major burden and is the fourth most common cancer diagnosed worldwide.[1] However, incidence is decreasing in many developed countries, leading to a reduction in the caseload of some centers and in the exposure of trainees.[2,3] The link between hospital case volume and survival improvement has been demonstrated in several cancers, including gynecologic malignancies.[4–10] Concerning cervical cancer, few studies have assessed the association between surgical volume and improved survival.[11–14]

A recent study aimed to analyze the association between surgical volume and survival of women with early-stage cervical cancer who underwent radical hysterectomy.[13] It concluded that hospital volume for radical hysterectomy may be a prognostic factor for early-stage cervical cancer–surgery performed at high-volume centers was associated with decreased risk of local recurrence and improved survival. However, this study reported some limitations, such as the use of a single-country national registry database, lack of information on surgical approach, and average volume calculated over 5 calendar years. In addition, improvement of outcomes may not be related only to superior quality of surgery, but also to adherence to guidelines and to the way multidisciplinary care is organized with the availability of imaging and postoperative radiotherapy.

Very recently, the SCCAN (Surveillance in Cervical Cancer) Consortium published two retrospective studies on the annual recurrence risk model for tailored surveillance strategy in patients with cervical cancer[15] and on postrecurrence survival in patients with cervical cancer.[16] The SCCAN Consortium consists of 20 tertiary care centers of excellence for the treatment of cervical cancer from Europe, Asia, North America, and Latin America. These centers have modern imaging modalities used for clinical staging (magnetic resonance imaging, expert ultrasonography, computed tomography, or positron emission tomography–computed tomography). All cases were discussed by a multidisciplinary team, surgery and pathology were performed by surgeons and pathologists with experience in gynecologic oncology, and institutional follow-up was performed by physicians. The present study aimed to assess the prognostic effect (defined in terms of disease-free and overall survival) of surgical volume per center for patients previously included in the SCCAN collaborative studies.

METHODS

SCCAN is an international, multicenter, retrospective study.[15] Patients were retrospectively included if they met the following inclusion criteria: 1) histologically confirmed cervical cancer treated between January 1, 2007, and December 31, 2016; 2) TNM stage T1a–T2b (based on preoperative assessment, American Joint Committee on Cancer); 3) primary surgical management; and 4) at least 1 year of follow-up data availability. Patients were treated in national referral centers for gynecologic oncology according to updated national or international guidelines.

For the present study, we selected patients with International Federation of Gynecology and Obstetrics (FIGO) 2009 stage IB1–IIA1 cervical cancer who underwent type B or C radical hysterectomy[17] who did not undergo neoadjuvant chemotherapy and had negative lymph nodes at final histology.

The protocol was approved by the IRB of the lead institution (General University Hospital, Prague, Czech Republic) in 2016. Institutional review board approval at the participating sites was a prerequisite for participation. The study was performed in accordance with the Declaration of Helsinki.

The principal investigator at each institution identified eligible patients, anonymized the data, and transferred the data using a web-based system to ensure consistent data collection, which ended in November 2020. Patients with missing information on key predictor variables, such as tumor and surgery characteristics (tumor type, tumor size) and details about follow-up (date of the last visit, disease status at the last visit, date of recurrence or death), were excluded.

STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines were followed in reporting results of this study.[18] Demographic and clinical data were summarized using mean±SD when considering quantitative variables and absolute counts and percentages if related to categorical items.

Disease-free survival was defined as the time interval between the date of surgery and evidence of the first disease progression or death from disease. *Overall survival* was defined as the time interval between the date of surgery and date of death from any cause. Both times were censored at the date of last follow-up if no event was observed.

The Kaplan–Meier method was used to estimate the distribution of time-to-event endpoints of disease-free survival and overall survival; differences among curves were assessed by the log-rank-test.[19,20] Cox[21] regression analysis was performed to estimate hazard ratios and their 95% CIs and to adjust for baseline risk factors.

Optimal cutoffs for surgical volume were identified using an unadjusted Cox proportional hazard model, with disease-free survival as outcome and defined as the value that minimizes the *P*-value of the split in groups in terms of disease-free survival. Number of radical hysterectomies was counted as an average over the entire study period per center.

Propensity score matching was used to adjust the differences between the two groups (high-volume and low- to middle-volume centers); a 1:1 ratio and the nearest-neighbor method was used without replacement and with a caliper of 0.2 SD of the propensity score distribution. Baseline variables used to formulate propensity scores included age, grade, lymphovascular space invasion (LVSI), pathologic stage, type of surgery, and maximum tumor diameter. Because residual differences in baseline covariates were observed, we performed a multivariable Cox model to better adjust surgical volume effect. SPSS 27.0 and R 4.1.2, library MatchIt were used.

RESULTS

Starting from a database of 4,343 patients, we initially included 2,157 (49.7%) patients according to inclusion criteria (baseline characteristics of the entire population are showed in Appendix 1, available online at http://links.lww.com/AOG/C965). Survival associated with continuous cutoffs of average number of radical hysterectomies performed in each center every year is demonstrated in Appendix 2, available online at http://links.lww.com/AOG/C965. The two most significant cutoffs for surgical volume were identified at 7 and 17 surgical procedures per center every year. We stratified the centers into three groups: centers performing fewer than seven radical hysterectomies per year were classified as *low volume*, those performing between 7 and 17 surgical radical hysterectomies per year were classified as *middle volume*, and those performing more than 17 radical hysterectomies per year were classified as *high volume*. In view of the difference in baseline characteristics of patients undergoing surgery at centers with different surgical volumes per year, a propensity score–matching analysis was performed grouping together low- and middle-volume compared with high-volume centers. After propensity score matching, 1,238 patients were analyzed–619 (50.0%) in high-volume centers, 523 (42.2%) in middle-volume centers, and 96 (7.8%) in low-volume centers. The exclusion process is shown in Figure 1.

Table 1 shows the clinical–pathologic characteristics of the patients analyzed after propensity score matching. Most patients were diagnosed with FIGO stage IB1 (n=1,145, 92.5%), squamous cell carcinoma (n=769, 62.1%), grade 2 (n=920, 74.3%), with negative LVSI (n=593, 47.9%) and underwent open radical hysterectomy (n=885, 71.5%). The majority of patients did not undergo adjuvant treatment after radical surgery (n=1,124, 90.8%). After propensity score matching, the only differences in baseline characteristics were found in grade (higher incidence of grade 3 in low- to middle-volume centers, $P<.001$) and LVSI (higher incidence of negative LVSI in low-volume centers, $P=.001$). Appendix 3, available online at http://links.lww.com/AOG/C965, shows the temporal matching of the three groups.

The median follow-up time of the included patients was 5.2 years (interquartile range 3.5–7.4). Five-year disease-free survival in the entire cohort was 90.6% (95% CI 88.8–92.4%), and 5-year overall survival was 96.4% (95% CI 95.2–97.6%). Of the entire cohort, 112 (9.0%) patients had recurrence and 48 (3.9%) died. A multivariable analysis performed on data from the 2,157 included patients before performing propensity score matching is demonstrated in Appendix 4, available online at http://links.lww.com/AOG/C965.

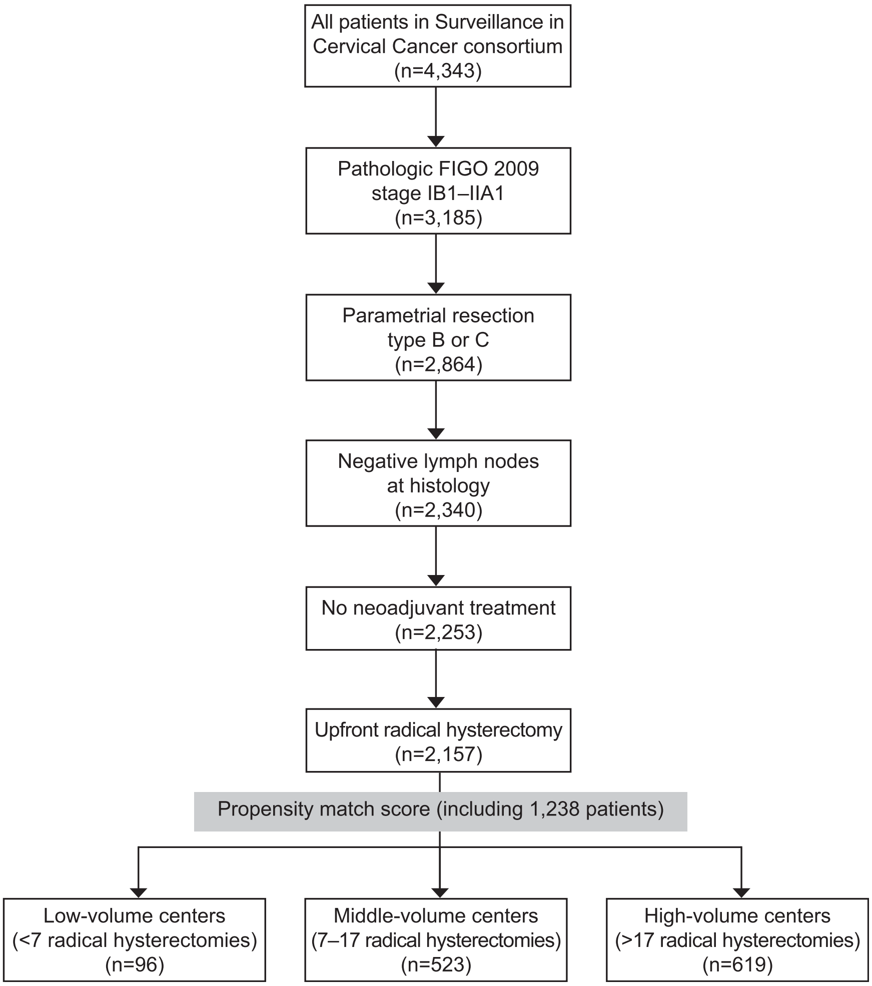

Fig. 1. Inclusion and exclusion process. FIGO, International Federation of Gynecology and Obstetrics.

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Patients who underwent surgery in higher-volume institutions had progressively better 5-year disease-free survival compared with those who underwent surgery in lower-volume centers (92.3% vs 88.9% vs 83.8%, P=.029) (Fig. 2). However, no difference in 5-year overall survival was noted among high-, middle-, and low-volume centers (95.9% vs 97.2% vs 95.2%, P=.70) (Fig. 3).

Table 2 demonstrates the Cox multivariable regression analysis for risk of recurrence in the propensity score–matched population. FIGO stage greater than IB1, presence of LVSI, grade greater than 1, tumor diameter greater than 20 mm, minimally invasive surgical approach, nonsquamous cell carcinoma histology, and lower-volume centers represented independent risk factors for recurrence. Table 3 shows the Cox multivariable regression analysis for risk of death in the propensity score–matched population. FIGO stage greater than IB1, presence of LVSI, tumor diameter greater than 20 mm, and nonsquamous cell carcinoma histology represented independent risk factors for death.

DISCUSSION

The present study aimed to assess the prognostic effect of radical hysterectomy volume in the SCCAN database, consisting of patients from 20 tertiary care international centers of excellence for the treatment of cervical cancer. We identified surgical volume of centers as an independent prognostic factor affecting disease-free survival. Higher number of radical hysterectomies performed in each center every year was associated with improved disease-free survival.

The favorable survival effect of treating patients with cancer in referral centers has already been demonstrated for multiple cancers,[4,5] including gynecologic malignancies.[6–10] Regarding cervical cancer, previous studies suggest a possible survival benefit for patients treated in high-volume centers.[11,13,14] Lee et al[12] report results from a meta-analysis showing comparable sur-

Table 1. Baseline Patient Characteristics After Propensity Score Matching

Characteristic	Total (N=1,238)	Center Volume			P
		High (n=619)	Middle (n=523)	Low (n=96)	
Age (y)	44.7±10.4	44.7±10.3	48.4±11.6	46.2±10.1	.89
Pathologic stage					.41
IB1	1,145 (92.5)	567 (91.6)	485 (92.7)	93 (96.9)	
IB2	68 (5.5)	38 (6.1)	27 (5.2)	3 (3.1)	
IIA1	25 (2.0)	14 (2.3)	11 (2.1)	0	
Histology					.18
Squamous	769 (62.1)	383 (61.9)	333 (63.7)	53 (55.2)	
Adenocarcinoma	395 (31.9)	193 (31.2)	168 (32.1)	34 (35.4)	
Adenosquamous	50 (4.0)	27 (4.4)	16 (3.1)	7 (7.3)	
Other	22 (1.8)	16 (2.5)	6 (1.2)	0	
Unknown	2 (0.2)	0	0	2 (2.1)	
Grade					<.001*
1	147 (11.9)	27 (4.4)	97 (18.5)	23 (24.0)	
2	920 (74.3)	540 (87.2)	334 (63.9)	46 (47.9)	
3	171 (13.8)	52 (8.4)	92 (17.6)	27 (28.1)	
LVSI					.001*
No	593 (47.9)	277 (44.7)	255 (48.8)	61 (63.5)	
Yes	345 (27.9)	169 (27.3)	159 (30.4)	17 (17.7)	
Unknown	300 (24.2)	173 (27.9)	109 (20.8)	18 (18.8)	
Diameter (mm)	20.4±11.9	20.2±12.1	20.6±11.7	19.8±11.1	.77
20 or less	761 (61.5)	379 (61.2)	319 (61.0)	63 (65.6)	.68
Greater than 20	477 (38.5)	240 (38.8)	204 (39.0)	33 (34.4)	
Surgical approach					.12
Open	885 (71.5)	429 (69.3)	390 (74.6)	66 (68.8)	
Other	353 (28.5)	190 (30.7)	133 (25.4)	30 (31.2)	
Adjuvant therapy					.62
No	1,124 (90.8)	557 (90.0)	479 (91.6)	88 (91.7)	
Yes	114 (9.2)	62 (10.0)	44 (8.4)	8 (8.3)	

LVSI, lymphovascular space invasion.
Data are mean±SD or n (%) unless otherwise specified.
* $P<.05$.

vival outcomes in low- and high-volume hospitals, but with a higher number of patients with poorer prognosis in the latter, and conclude that the benefit of hospital volume should be investigated in well-designed studies. Matsuo et al[13] conducted a large national registry database retrospective study demonstrating that hospital volume for radical hysterectomy may be a prognostic factor for early-stage cervical cancer and that surgery at high-volume centers was associated with decreased local recurrence risk and improved survival. A few differences between our study and the study from Matsuo et al[13] need to be highlighted. The proposed cutoffs were calculated based on the number of surgeries per center in a 5-year period. Moreover, the characteristics of the included patients were different–only 50% of patients had stage IB1 disease, 20% had parametrial involvement, 26% had metastatic lymph nodes, and almost 60% received adjuvant treatment. These might represent a limitation when analyzing the association of radical surgery with survival.

We tried to overcome the potential limitations of previous studies, such as the use of national registry databases, lack of information on surgical approach or analysis of a population treated with laparoscopic radical hysterectomy only (now identified as a well-known risk factor after publication of the LACC [Laparoscopic Approach to Cervical Cancer] Trial results[22]), and lack of cutoff based on number of surgeries per year.[12–14] Particularly with regard to surgical approach, we have to highlight that, in the present study, minimally invasive approaches were associated with a significant risk of recurrence, but not death, in multivariable analysis (Tables 2 and 3).

With the use of propensity score–matching analysis, we tried to adjust for the potential differences between baseline groups. However, patients in the high-volume group still had a higher incidence of LVSI, whereas those in the low-volume group had a higher incidence of grade 3 tumors. These discrepancies could have affected our findings. Our

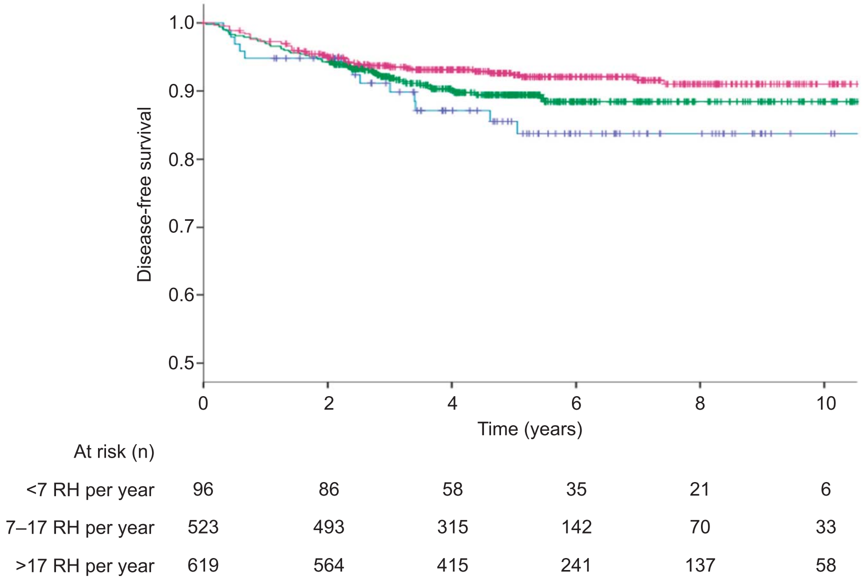

Fig. 2. Disease-free survival comparison in patients undergoing radical hysterectomy (RH) in high-volume, middle-volume, and low-volume centers (P=.029). *Blue line* indicates fewer than seven RH/year; *green line* indicates 7–17 RH/year; *purple line* indicates more than 17 RH/year.

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propensity score–matching survival analysis showed that patients who underwent surgery in centers performing more than 17 radical hysterectomies per year had better disease-free survival. This finding was confirmed in multivariable analysis. The lack of difference in overall survival may be explained by the relatively low number of events in the included patients (48 deaths, 3.9%). With our results, we aim to define a minimum number of radical hysterectomies per year used to describe a center as high-volume. The need for the identification of a "safe" minimum number of procedures per year was one of the topics discussed in the European Society of Gynaecological Oncology quality indicators for surgical treatment of cervical cancer.[23]

There is a clear link between the volume of centers and surgeons' learning curve and proficiency. A recent study demonstrates that surgeon experience was an independent prognostic factor in the outcome of minimally invasive radical hysterectomy, with a minimum of 18 radical hysterectomies per surgeon as the threshold for improved survival.[24] This hypothesis was also confirmed in cases of open radical hysterectomy.[25]

To quantify surgical activity across Europe, it should be reported that, in a previously published

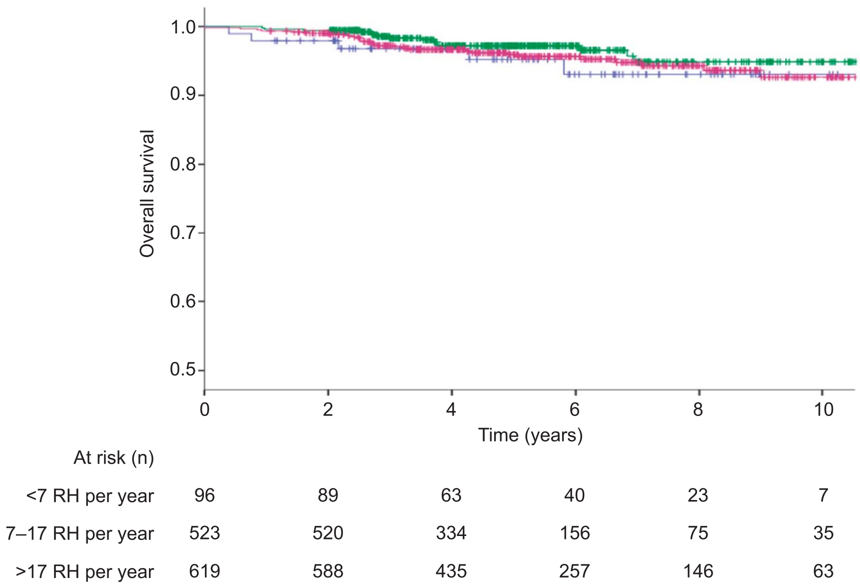

Fig. 3. Overall survival comparison in patients undergoing radical hysterectomy (RH) in high-volume, middle-volume, and low-volume centers (P=.070). *Blue line* indicates fewer than seven RH/year; *green line* indicates 7–17 RH/year; *purple line* indicates more than 17 RH/year.

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Table 2. Proportional Hazard Model for Disease-Free Survival After Propensity Score Matching

	Multivariable	*P*
Age (y)	1.01 (0.99–1.03)	.35
Stage		.03*
1b1	1.00	
1b2	2.18 (1.16–4.08)	
2a1	2.00 (0.73–5.52)	
LVSI		.005*
No	1.00	
Yes	1.79 (1.15–2.78)	
Unknown	0.82 (0.48–1.43)	
Grade		.002*
1	1.00	
2	4.14 (1.63–10.54)	
3	2.08 (0.71–6.12)	
Adjuvant therapy		.99
No	1.00	
Yes	1.00 (0.59–1.70)	
Diameter (mm)		<.001*
20 mm or less	1.00	
Greater than 20	2.32 (1.53–3.51)	
Surgical approach		<.001*
Open	1.00	
Other	2.65 (1.78–3.95)	
Histotype		.003*
Squamous	1.00	
Adenocarcinoma	1.27 (0.81–1.99)	
Other	2.77 (1.53–5.02)	
No. of radical hysterectomies/y		.001*
Fewer than 7	1.00	
7–17	0.58 (0.31–1.09)	
More than 17	0.32 (0.17–0.61)	

LVSI, lymphovascular space invasion.
Data are hazard ratio (95% CI) unless otherwise specified.
* *P*<.05.

Table 3. Proportional Hazard Model for Overall Survival After Propensity Score Matching

	Multivariable	*P*
Age (y)	1.02 (0.99–1.05)	.11
Stage		.004*
1b1	1.00	
1b2	3.90 (1.76–8.64)	
2a1	1.31 (0.18–9.75)	
LVSI		.045*
No	1.00	
Yes	1.98 (1.01–3.91)	
Unknown	0.82 (0.35–1.92)	
Grade		.30
1	1.00	
2	3.03 (0.68–13.42)	
3	2.22 (0.42–11.62)	
Adjuvant therapy		.67
No	1.00	
Yes	1.18 (0.56–2.46)	
Diameter (mm)		<.001*
20 or less	1.00	
Greater than 20	2.08 (1.07–4.03)	
Surgical approach		.054
Open	1.00	
Other	1.88 (0.99–3.57)	
Histotype		.008*
Squamous	1.00	
Adenocarcinoma	1.42 (0.69–2.92)	
Other	3.19 (1.35–7.55)	
No. of radical hysterectomies/y		.27
Fewer than 7	1.00	
7–17	0.43 (0.15–1.21)	
More than 17	0.55 (0.20–1.48)	

LVSI, lymphovascular space invasion.
Data are hazard ratio (95% CI) unless otherwise specified.
* *P*<.05.

European Society of Gynaecological Oncology survey on clinical practice in cervical cancer surgery, only 8% of centers reported performing fewer than five radical hysterectomies annually, 26% of centers reported performing 10–20, and about 50% of centers reported performing more than 20.[26] Furthermore, it should be highlighted that the inclusion criteria in the present study might have led to an underestimation of the number of radical hysterectomies per center per year. In our cohort, we excluded patients who underwent radical hysterectomy but had unexpected lymph node metastasis on final pathology and those who underwent hysterectomy after neoadjuvant chemotherapy. As a result, the actual threshold for the number of radical hysterectomies per year that is associated with better outcome may be slightly higher.

We have to recognize a few limitations of the present study–first of all, the retrospective nature of the analysis. Secondly, there were minor differences in patients' baseline characteristics, even after propensity score matching. Thirdly, data on LVSI were missing in 24.2% of cases. Moreover, only 3 of the 20 (15%) centers performed more than 17 radical hysterectomies per year and were considered high-volume centers. There was a lack of information on individual surgeon volume and number of surgeons per center. Lastly, we did not report information about perioperative morbidity. On the other hand, we note that the present study overcomes limitations such as a single-country or national registry database and lack of information on surgical approach, and we defined a calculated cutoff of number of cases per year to categorize center volume. Moreover, this study recorded data from preselected academic referral centers adhering to national and international guidelines.

Surgical volume of centers represented an independent prognostic factor affecting disease-free survival in the present retrospective analysis. Increasing number of radical hysterectomies performed in each center every year was associated with improved disease-free survival (but not overall survival).

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