The impact of hospital surgical volume on survival in early-stage cervical cancer treated with radical hysterectomy: a sub-analysis of the SCCAN collaborative retrospective cohort study.

Abstract

Objective: To evaluate the impact of number of radical hysterectomies performed per year in each center on disease-free survival (DFS) and overall survival (OS), from patients previously included in the SCCAN collaborative studies.

Methods: International, multicenter, retrospective study. Patients with FIGO 2009 stage IB1-IIA1 cervical cancer who underwent radical hysterectomy, did not undergo neo-adjuvant chemotherapy and with negative lymph nodes at final histology, were included. Patients were treated in national referral centers for gynecologic oncology according to updated national/international guidelines. Optimal cut-offs for surgical volume were identified using an unadjusted Cox proportional hazard model with DFS as outcome and defined as the value which minimizes the p-value of the split in groups in terms of DFS. A Propensity Score Matching (PSM) was used to adjust the differences between the groups baseline characteristics.

Results: 2,157 patients were initially included. The two most significant cut-offs for surgical volume were identified in 7 and 17 surgical procedures, dividing the entire cohort in low, middle, and high-volume centers. After the PSM, 1,238 patients, distributed as 619 (50.0%) in high volume, 523 (42.2%) in middle volume and 96 (7.8%) in low volume group, were analyzed. Patients operated in higher volume institutions had a progressively better 5-year DFS than those operated in lower volume centers (92.3% vs 88.9% vs 83.8%, p=0.029). No 5-year OS difference was noted (95.9% vs 97.2% vs 95.2%, p=0.70). Cox multivariable regression analysis showed that FIGO stage >IB1, presence of LVSI, grade >1, tumor diameter >20 mm, minimally invasive surgical approach, non-squamous cell carcinoma histology, and lower volume centers represented independent risk factors for recurrence.

Conclusion: Surgical volume of centers represented an independent prognostic factor affecting DFS. Increasing number of radical hysterectomies performed in each center every year was associated with improved DFS. Performance of more than 17 radical hysterectomies per year may be considered the target volume of cases for referral centers associated with better DFS.

Introduction

Despite the introduction and the implementation of screening and vaccination programs, cervical cancer remains a major burden being the fourth most common cancer diagnosed worldwide [1]. However, the incidence of uterine cervical cancer is decreasing in many developed countries, leading to a reduction of the caseload of some centers and of the exposure of trainees [2,3]. The link between hospital case volume and survival improvement has been demonstrated in several cancers, including gynecological malignancies [4-10]. Concerning cervical cancer, few studies assessed the association between surgical volume and improved survival [11-14]. Particularly, 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, as 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 five 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 Surveillance in Cervical Cancer (SCCAN) consortium has published two retrospective studies on the annual recurrence risk model for tailored surveillance strategy in patients with cervical cancer [15] and on the post-recurrence survival in patients with cervical cancer [16]. The SCCAN study consortium consisted of 20 tertiary centers of excellence for the treatment of cervical cancer from Europe, Asia, North America, or Latin America. These centers have modern imaging modalities used for clinical staging (magnetic resonance imaging, expert ultrasound, computed tomography, or positron emission tomography/computed tomography). All cases were prospectively collected and discussed by a multidisciplinary team, surgery and pathology were performed by surgeon and pathologist with experience in gynecologic oncology, and institutional follow-up was performed by physicians.

The present study aimed to assess the prognostic impact (defined in terms of disease-free and overall survival) of surgical volume per center, from patients previously included in the SCCAN collaborative studies.

Methods

The SCCAN is an international, multicenter, retrospective study [15]. Patients were retrospectively included if they met the following inclusion criteria: (i) histologically confirmed cervical cancer treated between 01st January 2007 and 31st December 2016; (ii) TNM stage T1a-T2b (based on the preoperative assessment; American Joint Committee on Cancer e Cervix Uteri Cancer Staging); (iii) primary surgical management, including fertility-sparing procedures/surgical treatment after neoadjuvant chemotherapy; (iv) and at least one year of follow-up data availability (patient underwent surgery >1 years before last or follow-up visit or was not lost to follow-up during the first year after surgery). Patients were treated in national referral centers for gynecologic oncology according to updated national/international guidelines.

For the present study we selected patients with FIGO 2009 stage IB1-IIA1 who underwent radical hysterectomy with parametrectomy type B or C, who did not undergo neo-adjuvant chemotherapy and with negative lymph nodes at final histology.

The protocol was approved by the institutional review board of the lead institution (General University Hospital in 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. The type of parametrial resection of radical hysterectomy was classified using the Querleu-Morrow-modified classification system [17].

Patients with missing information on key predictor variables, such as tumor and surgery characteristics (tumor type, tumor size), and details about the follow up (date of the last visit, disease status at the last visit and date of recurrence/death) were excluded.

Statistical analysis

STROBE guidelines were followed in reporting results of this study [18]. Demographics and clinical data were summarized using mean and standard deviation (SD) when considering quantitative variables and absolute counts and percentages if related to categorical items.

Disease-Free Survival (DFS) was defined as the time interval between the date of surgery and the evidence of the first disease progression or death from disease. Overall Survival (OS) 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 end points of DFS and OS and differences among curves were assessed by the log-rank-test [19,20].

Cox regression analysis was performed to estimate Hazard Ratios (HR) and their 95% confidence intervals and to adjust for baseline risk factors [21].

Optimal cut-offs for surgical volume were identified using an unadjusted Cox proportional hazard model with DFS as outcome and defined as the value which minimizes the p-value of the split in groups in terms of DFS. Number of radical hysterectomies was counted as average over the entire study period per center.

A Propensity Score Matching (PSM) was used to adjust the differences between the two groups (high-volume and low-middle volume centers); a ratio 1:1 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, lymph-vascular space invasion (LVSI), pathological stage, type of surgery, maximum tumor diameter. As residual differences in baseline covariates were observed we performed a multivariable Cox model to better adjust surgical volume effect. IBM SPSS statistical software v. 27.0 and R v. 4.1.2, library MatchIt were used.

Results

Patients' characteristics

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). Survival associated with continuous cut-offs of average number of radical hysterectomies performed in each center every year is demonstrated in Appendix 2. The two most significant cut-offs for surgical volume were identified at 7 and 17 surgical procedures per center every year. We stratified the centers in three groups: centers performing less than 7 radical hysterectomies per year were classified as "low volume", those performing between 7 and 17 surgical procedures per year as "middle volume" and those performing more than 17 radical hysterectomy per year as "high volume". In view of the difference in baseline characteristics of patients with different surgical volume per year, a PSM analysis was performed, grouping together low and middle versus high volume. After the PSM, 1,238 patients, distributed as 619 (50.0%) in high volume, 523 (42.2%) in middle volume and 96 (7.8%) in low volume group, were analyzed. Exclusion process is demonstrated in Figure 1.

Table 1 shows the clinico-pathological characteristics of the patients analyzed after PSM. Most of 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%). Majority of patients did not undergo adjuvant treatment after radical surgery (1,124, 90.8%). After PSM the only differences in baseline characteristics were found in grade (higher incidence of grade 3 in low-middle volume centers, p<0.0001) and LVSI (higher incidence of negative LVSI in low volume centers, p=0.001). Appendix 3 shows the temporal matching of the three groups.

Survival analysis in PSM patients

The median follow-up time of the included patients was 5.2 years (IQR: 3.5-7.4). 5-year DFS in the entire cohort was 90.6% (95%CI, 88.8%-92.4%) and 5-year OS was 96.4% (95%CI, 95.2%-97.6%). 112 (9.0%) patients had recurrence and 48 (3.9%) patients died in the entire cohort.

A multivariable analysis performed on the 2,157 included patients before performing PSM is demonstrated in Appendix 4.

Patients operated in higher volume institutions had a progressively better 5-year DFS compared to those operated in lower volume centers (92.3% vs 88.9% vs 83.8%, p=0.029) (Figure 2). However, no 5-year OS difference was noted between high, middle, and low volume centers (95.9% vs 97.2% vs 95.2%, p=0.70) (Figure 3).

Table 2 demonstrates the Cox multivariable regression analysis for risk of recurrence in the PSM population. FIGO stage >IB1, presence of LVSI, grade >1, tumor diameter >20 mm, minimally invasive surgical approach, non-squamous 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 PSM population. FIGO stage >IB1, presence of LVSI, tumor diameter >20 mm and non-squamous cell carcinoma histology represented independent risk factors for death.

Discussion

The present study aimed to assess the prognostic impact of radical hysterectomies volume per center per year in the SCCAN database consisting of patients from 20 tertiary international centers of excellence for the treatment of cervical cancer. It identified surgical volume of centers as an independent prognostic factor affecting DFS. Increasing number of radical hysterectomies performed in each center every year was associated with improved DFS.

The favorable survival impact of treating oncologic patients in referral centers has already been demonstrated for multiple cancers [4,5], including gynecological malignancies [6-10]. Regarding cervical cancer, previous studies suggested a possible survival benefit for patients treated in large volume centers [11,13,14]. Lee et al. [12] reported results from a meta-analysis showing comparable survival outcomes in

low and high-volume hospitals, but with higher number of patients with poorer prognosis in the latter, and concluded 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. Few differences between our study and the one from Matsuo et al. [13] need to be highlighted. The proposed cut-offs were calculated based on the number of surgeries per center in a five-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% of patients received adjuvant treatment. These might represent a limitation when analyzing the impact of radical surgery on 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 defined as a well-known risk factor, after LACC trial results have been published [22]) and lack of cut-off based on surgeries per year [12-14]. Particularly, with regards to the surgical approach, we have to highlight that in the present study, minimally invasive approaches were associated with a significant risk of recurrence at multivariable analysis.

With the use of PSM analysis we tried to adjust for the potential difference between patients operated in high or low volume hospitals. However, even after PSM, patients in the high-volume centers group had higher incidence of LVSI positivity. On the other side, patients in the low volume group had higher incidence of grade 3 tumors. The prognostic impact of grade, however, has not been universally accepted and updated guidelines do not support the use of adjuvant treatment based on the presence of high grade disease [23-25]. Our survival analysis showed that patients operated in centers performing more than 17 radical hysterectomies per year had better DFS (despite higher incidence of poorer prognostic factors such as LVSI). This has been confirmed even in multivariable analysis which takes into accounts all prognostic variables impacting on DFS. The lack of OS difference 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 define 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 (ESGO) quality indicators for surgical treatment of cervical cancer [26].

Our results illustrate the importance of referring patients to high volume centers. It reflects the significance of surgical training and skills of gynecologic oncology teams working in high volume centers, ensuring adequate and frequent exposure and practice. There is a clear link between the volume of centers and the surgeons' learning curve and proficiency. A recent study demonstrated that surgeon's experience was an independent prognostic factor in the outcome of minimally invasive radical hysterectomy, with a minimum of 18 radical hysterectomies per surgeon as threshold for an improved survival [27]. This hypothesis was confirmed also in case of open radical hysterectomy [28].

In order to quantify the surgical activity across Europe, it should be reported that in a previously published ESGO survey on clinical practice in cervical cancer surgery, only 8% of institutions reported less than 5, 26% of centers performed 10-20, and about 50% reported more than 20 radical parametrectomies annually [29]. Therefore, a cut-off of 17 radical hysterectomies per year seems to be a feasible target for referral centers.

Furthermore, it should be highlighted that the inclusion criteria in the present study might have led to an underestimation of the number of radical surgeries per center per year. In our cohort we excluded those patients who had a radical hysterectomy but had unexpected lymph node metastasis on final pathology and patients who had a hysterectomy after neo-adjuvant 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.

Potentially not only survival, but also peri-operative morbidity may be improved in patients treated by high volume centers/surgeons. In fact, a meta-analysis showed that patients treated in high volume centers had a tendency toward shorter operation time and lower estimated blood loss, though no difference in intra- and post-operative complications as well as length of hospital stay was noted [12]. Similarly, a large study by Wright et al. showed that, after adjustment for case mix and surgeon volume, hospital volume had no

independent effect on morbidity and mortality [30]. The same study demonstrated that patients treated by high-volume surgeons may have fewer postoperative medical complications, shorter lengths of stay, and lower transfusion requirements, showing that surgeon's volume, rather than hospital volume impacted on peri-operative morbidity outcomes.

We have to recognize few limitations of the present study. First of all, the retrospective nature of the analysis. Secondly, the baseline patients' characteristics had few minor differences even after PSM (even though these differences were balanced between the two groups and results confirmed in multivariable analysis). Thirdly, data on LVSI was missing in 24.2% of cases. Moreover, only 3/20 (15%) centers performed more than 17 radical hysterectomies per year and were considered high volume. Lastly, we did not report information about peri-operative morbidity. On the other hand, we acknowledge the fact that the present study overcomes limitations such as single country/national registry database, lack of information on surgical approach and the fact we defined a calculated cut-off of number of cases per year to define centers volume. Moreover, this study recorded data from pre-selected referral centers adhering to national/international guidelines.

Conclusion

Surgical volume of centers represented an independent prognostic factor affecting DFS in the present retrospective analysis. Increasing number of radical hysterectomies performed in each center every year was associated with improved DFS (but not OS). Performance of at least 18 radical hysterectomies per year may be considered the target volume of cases for referral centers associated with DFS improvement.

Acknowledgments

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Table 1. Baseline patients' characteristics after propensity score matching .

	Total (N=1238)	High-volume centers (N=619)	Mid-volume centers (N=523)	Low-volume centers (N=96)	P-value
Age (years) (mean ± SD)	44.7 ±10.4	44.7 ± 10.3	48.4 ± 11.6	46.2 ± 10.1	0.89
Pathological stage					0.41
IB1	1145 (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					0.18
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%)	
Others	22 (1.8%)	16 (2.5%)	6 (1.2%)	0	
Unknown	2 (0.2%)	0	0	2 (2.1%)	
Grade					<0.0001*
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					0.001*
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) (mean ± SD)	20.4±11.9	20.2 ± 12.1	20.6 ± 11.7	19.8 ± 11.1	0.77
Diameter					0.68
≤ 20 mm	761 (61.5%)	379 (61.2%)	319 (61.0%)	63 (65.6%)	
> 20 mm	477 (38.5%)	240 (38.8%)	204 (39.0%)	33 (34.4%)	
Surgical Approach					0.12
Open	885 (71.5%)	429 (69.3%)	390 (74.6%)	66 (68.8%)	
Others	353 (28.5%)	190 (30.7%)	133 (25.4%)	30 (31.2%)	
Adjuvant therapy					0.62
No	1124 (90.8%)	557 (90.0%)	479 (91.6%)	88 (91.7%)	
Yes	114 (9.2%)	62 (10.0%)	44 (8.4%)	8 (8.3%)	

*p<0.05

Table 2. Proportional hazard model after propensity score matching for disease-free survival

	MULTIVARIABLE HR (95% CI)	
Age in years	1.01 (0.99-1.03)	p=0.35
Stage		p=0.03*
1b1	1.00	
1b2	2.18 (1.16-4.08)	
2a1	2.00 (0.73-5.52)	
LVSI		p=0.005*
No	1.00	
Yes	1.79 (1.15-2.78)	
unknown	0.82 (0.48-1.43)	
Grade		p=0.002*
1	1.00	
2	4.14 (1.63-10.54)	
3	2.08 (0.71-6.12)	
Adjuvant therapy		p=0.99
No	1.00	
Yes	1.00 (0.59-1.70)	
Diameter		p<0.0001*
≤ 20 mm	1.00	
> 20 mm	2.32 (1.53-3.51)	
Surgical Approach		p<0.0001*
Open	1.00	
Others	2.65 (1.78-3.95)	
Histotype		p=0.003*
Squamous	1.00	
Adenocarcinoma	1.27 (0.81-1.99)	
Other	2.77 (1.53-5.02)	
Volume per year		p=0.001*
<7	1.00	
7-17	0.58 (0.31-1.09)	
>17	0.32 (0.17-0.61)	

*p<0.05

Table 3. Proportional hazard model after propensity score matching for overall survival

	MULTIVARIABLE HR (95% CI)	
Age in years	1.02 (0.99-1.05)	p=0.11
Stage		p=0.004*
1b1	1.00	
1b2	3.90 (1.76-8.64)	
2a1	1.31 (0.18-9.75)	
LVSI		P=0.045*
No	1.00	
Yes	1.98 (1.01-3.91)	
unknown	0.82 (0.35-1.92)	
Grade		p=0.30
1	1.00	
2	3.03 (0.68-13.42)	
3	2.22 (0.42-11.62)	
Adjuvant therapy		p=0.67
No	1.00	
Yes	1.18 (0.56-2.46)	
Diameter		p<0.0001*
≤ 20 mm	1.00	
> 20 mm	2.08 (1.07-4.03)	
Surgical Approach		p=0.054
Open	1.00	
Others	1.88 (0.99-3.57)	
Histotype		p=0.008*
Squamous	1.00	
Adenocarcinoma	1.42 (0.69-2.92)	
Other	3.19 (1.35-7.55)	
Volume per year		p=0.27
<7	1.00	
7-17	0.43 (0.15-1.21)	
>17	0.55 (0.20-1.48)	

*p<0.05

Figures' legends.

Figure 1. Inclusion and exclusion process.

Figure 2. Disease-free survival comparison in patients undergoing radical hysterectomy in high versus middle versus low volume centers (p=0.029).

Figure 3. Overall survival comparison in patients undergoing radical hysterectomy in high versus middle versus low volume centers (p=0.070).