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Original Article

Association between hospital treatment volume and survival of women with gynecologic malignancy in Japan: a JSOG tumor registry-based data extraction study

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Our study used the JSOG database. The JSOG forbids the transfer, rent, or sale of the data to any third party without prior approval. For inquiries about access to the data, JGOG can be contacted via the following phone number: +81-03-5206-1982.

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ABSTRACT

Objective: Associations between hospital treatment volume and survival outcomes for women with 3 types of gynecologic malignancies, and the trends and contributing factors for high-volume centers were examined.
Methods: The Japan Society of Obstetrics and Gynecology tumor registry databased retrospective study examined 206,845 women with 80,741, 73,647, and 52,457 of endometrial, cervical, and ovarian tumor, respectively, who underwent primary treatment in Japan between 2004 and 2015. Associations between the annual treatment volume and overall survival (OS) for each tumor type were examined using a multivariable Cox proportional hazards model with restricted cubic splines. Institutions were categorized into 3 groups (low-, moderate-, and high-volume centers) based on hazard risks.
Results: Hazard ratio (HR) for OS each the 3 tumors decreased with hospital treatment volume. The cut-off points of treatment volume were defined for high- (≥50, ≥51, and ≥27), moderate- (20–49, 20–50, and 17–26), and low-volume centers (≤19, ≤19, and ≤16) by cases/year for endometrial, cervical, and ovarian tumors, respectively. Multivariate analysis revealed younger age, rare tumor histology, and initial surgical management as contributing factors for women at high-volume centers (all, p<0.001). The proportion of high-volume center treatments decreased, whereas low-volume center treatments increased (all p<0.001). Treatment at high-volume centers improved OS than that at other centers (adjusted HR [aHR]=0.83, 95% confidence interval [CI]=0.78–0.88; aHR=0.78, 95% CI=0.75–0.83; and

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

Author Contributions
Conceptualization: M.H., M.K., O.K., A.D., E.T., O.A., K.H., N.S., [1]M.M., Y.N., Y.W., [2]M.M.; Data curation: M.H., Y.W., [2]M.M.; Formal analysis: M.H., O.K.; Funding acquisition: [2]M.M.; Investigation: M.H., A.D., E.T., O.A., K.H., N.S., [1]M.M., Y.N., Y.W., [2]M.M.; Methodology: M.H., M.K., O.K., A.D., E.T., O.A., K.H., N.S., [1]M.M., Y.N., Y.W., [2]M.M.; Project administration: M.H., M.K., A.D., E.T., O.A., K.H., N.S., [1]M.M., Y.N., Y.W., [2]M.M.; Software: M.H.; Supervision: M.K., O.K., A.D., E.T., O.A., K.H., N.S., [1]M.M., Y.N., Y.W., [2]M.M.; Validation: M.H., M.K.; Visualization: M.H.; Writing - original draft: M.H., M.K., O.K., A.D., E.T., O.A., K.H., N.S., [1]M.M., Y.N., Y.W., [2]M.M.; Writing - review & editing: M.H., M.K., O.K., A.D., E.T., O.A., K.H., N.S., [1]M.M., Y.N., Y.W., [2]M.M.
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aHR=0.90, 95% CI=0.86–0.95 for endometrial, cervical, and ovarian tumors).
Conclusion: Hospital treatment volume impacted survival outcomes. Treatments at high-volume centers conferred survival benefits for women with gynecologic malignancies. The proportion of treatments at high-volume centers have been decreasing recently.

Keywords: Endometrial Cancer; Cervical Cancer; Ovarian Cancer; Hospital, high-volume; Survival

Synopsis
For women with gynecologic malignancy, hospital treatment volume had an impact on survival outcome. The practice pattern shifted with scattering of patients and treatments at high-volume centers were decreasing. High-volume centers in Japan were associated with improved overall survival of gynecologic malignancies.

INTRODUCTION

Approximately 1.3 million women are estimated to be newly diagnosed with gynecologic cancer every year worldwide. The predicted annual totals in 2018 were 569,847, 382,069, and 295,414 for cervical, endometrial, and ovarian cancers, respectively [1]. Approximately 378,142 women are estimated to be newly diagnosed with gynecologic cancers, including 136,151 (36.0%), 121,483 (32.1%), and 110,798 (29.3%) endometrial, cervical, and ovarian cases, respectively, in Japan from 2004–2015 [2]. Age-adjusted incidence rates for endometrial cancer per 100,000 persons in Japan from 2004–2015 have increased from 11.1 to 22.8, whereas that for cervical and ovarian cancers have remained stable (15.5 and 14.2, respectively). Additionally, the 5-year overall survival (OS) rates of women in Japan with 3 major types of gynecologic malignancies have improved during the same period—79.8% to 81.3%, 72.2% to 76.5%, and 55.0% to 60.0% for endometrial, cervical, and ovarian cancers, respectively [2,3].

Treatment for gynecologic malignancies includes hysterectomy with or without bilateral salpingo-oophorectomy and nodal evaluation, radiotherapy, and chemotherapy, depending on tumor type, cancer stage, and patient status. For treatments of gynecologic malignancies in Japan, the public medical insurance program is applied to all Japanese citizens, which covers standard treatments. The program provides patients with gynecologic oncologist appointments and cancer treatments at leading hospitals and/or designated regional cancer centers through medical referral assistance services, including a coordinate with the local attending doctor and patient's referral.

Practicing guideline adherence and receiving surgery by skilled surgeons at a high-volume center are associated with improved survival outcomes in certain cancer types [4-6]. Since 2007, the Ministry of Health, Labor, and Welfare (MHLW) in Japan has established the “Promote Cancer Control Programs”, an important constantly addressed policy aimed at reducing disparities in cancer treatments [7]. However, there are limited data on the disparities and facility attributes in gynecologic cancer treatments that may be associated with survival outcomes in Japan. Moreover, there remains a paucity of high-quality evidence on the relationship between hospital treatment volume and survival outcomes in gynecologic malignancies.

Therefore, the primary objective of this study was to examine the characteristics of women who underwent initial treatment at high-treatment volume centers in Japan for 3 major gynecologic malignancies: endometrial, cervical, and ovarian tumors. The secondary objective was to examine survival outcomes of women for these 3 major gynecologic malignancies in hospital with high-, moderate-, and low-treatment volumes.

MATERIALS AND METHODS

1. Study design and patient selection

This retrospective observational study used the Japan Society of Obstetrics and Gynecology (JSOG) database, a publicly available and deidentified database, with prior approval. The JSOG tumor registry database is a national, hospital-based gynecologic cancer registry launched in 2001, supported and managed by the gynecologic tumor committee of the JSOG. Approximately 60% of all newly diagnosed gynecologic malignancies in Japan are recorded in the database [3]. In 2015, the database included information from 430 JSOG-accredited hospitals; among them, 275 (64.0%) centers were designated regional cancer centers managed by the MHLW [8].

The database records the following comprehensive information of women with initial treatment for 3 major gynecologic malignancies (endometrial, cervical, and ovarian tumor), irrespective of out- or in-patient status: cancer types, tumor characteristics, treatment types, and survival outcomes [9]. All participating centers adhered to the same definition and submitted the data annually to the JSOG committee using the same online format. For missing or duplicate data in the database, the JSOG central control center made appropriate inquiries with each center. This study was approved by the Tokai University School of Medicine (hosting institution) Institutional Review Board and the JSOG Ethics Committee, which has authority to approve studies conducted using the JSOG tumor registry data.

All data, including gynecologic malignancy treatment volume, were obtained from the JSOG tumor registry database alone. Cases recorded in the section for “endometrial tumor”, “cervical tumor”, and “ovarian tumor”, limited to the primary malignancy, were obtained. Within the extracted dataset, the study population included women with invasive gynecologic malignancies of 3 major types (endometrial, cervical, or ovarian tumors) who had undergone initial treatment from 2004–2015. Women with ovarian borderline malignancies were excluded. Data from 2001–2003 were excluded due to missing information on the detailed treatment procedure.

2. Clinical information

Collected covariates included institution number, patient demographics, tumor characteristics, and treatment types. Patient demographics include age (<40, 40–49, 50–59, 60–69, ≥70 years), year (2004–2007, 2008–2011, 2012–2015), and registry area (north, east, central, west/south), as previously defined [10]. Institution demographics included hospital treatment volumes (high, moderate, low), their annual averages, and designated regional cancer hospital (yes or no). Tumor characteristics included cancer stage and histological type (endometrial tumor: type 1, including grade 1 and 2 endometrioid adenocarcinomas; type 2, including all endometrial adenocarcinomas that are not type 1 [such as serous, clear cell, undifferentiated]; and grade 3 endometrioid carcinoma; and other tumors [such as sarcoma]; cervical cancer: squamous, adenocarcinoma, and others; ovarian cancer: serous

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adenocarcinoma, non-serous adenocarcinoma, and other tumors, including germ cell tumor, sex cord stromal tumor, and sarcoma). Treatment types included initial treatment type (surgery, radiotherapy including concurrent chemoradiation, chemotherapy, and others), lymphadenectomy (performed versus not performed/unknown), and adjuvant treatment for initial surgical cases (performed versus not performed/unknown). The JSOG database collects information about initial treatments, and the method for counting the treatments for each case was described in order. For example, women treated with neoadjuvant chemotherapy followed by surgery and postoperative adjuvant chemotherapy were described as method 1: chemotherapy; method 2: surgery; and method 3: chemotherapy. Survival outcomes include follow-up time, vital status, and cause of death.

3. Study definition

In this study, gynecologic malignancy was defined as endometrial, cervical, or ovarian malignancy. The designated regional cancer hospital was assigned by the MHLW [8]. Cancer stages are classified based on the 2008 International Federation of Gynecology and Obstetrics (FIGO) staging system for endometrial and cervical cancers and the 2014 FIGO staging system for ovarian cancer [11,12]. The average annual hospital treatment volume is calculated as the number of women with each gynecologic cancer treated at a given institution divided by the number of years the institution have participated in the JSOG tumor registry database. OS is defined as the time interval between cancer diagnosis and death. Cases without a survival event or those lost to follow-up were censored at the last visit with known vital status.

4. Validation of hospital treatment volume grouping

To determine the hospital treatment volume group for each gynecologic malignancy (endometrial, cervical, and ovarian tumor), a multivariate Cox proportional hazard model with restricted cubic splines was performed (**Fig. 1A-C**). The corresponding log hazard ratio (HR) was plotted against the annual hospital treatment volume [13]. This reflects the relationship between all-cause death and annual hospital treatment volume after adjustment for covariates, including age, area, year, cancer stage, pathology, and initial treatments. The use of a restricted cubic spline allows for flexible multivariable model, accounting for the nonlinear relationship between survival and the average annual treatment volume without assuming the location or existence of potential cut-off points [14]. To better define the relationship between annual hospital treatment volume and survival, a 5-knot model was adopted due to its large sample size. Alternative models were examined, including 4- and 3-knot models and adapted splines (**Table S1**). The final model selection was based on the Akaike information criteria [15]. The model identified 2 ranges of annual treatment hospital treatment volumes that correspond to changes in the log HR.

Additional analysis was performed to examine the robustness of the model using the Joinpoint Regression Program (National Institute of Health, Bethesda, MD, USA) [16]. Potential changes were found in the HR based on the annual hospital treatment volume. These cut-off values were similar to the 5-knot points. Linear segmented regression analysis showed cases related to the HR change. Among women with endometrial and cervical malignancies, the log HR decreased linearly as the annual hospital treatment volume increased until approximately 50 cases; thereafter, it remained consistent. Among women with ovarian malignancy, the log HR remained stable until approximately 17 cases; thereafter, it decreased linearly as the annual hospital treatment volume increased to between 18 and 45 cases (**Fig. 1A-C**). Based on the cut-off points, the institutions were categorized as high- (≥50, ≥51, and ≥27 cases/year for

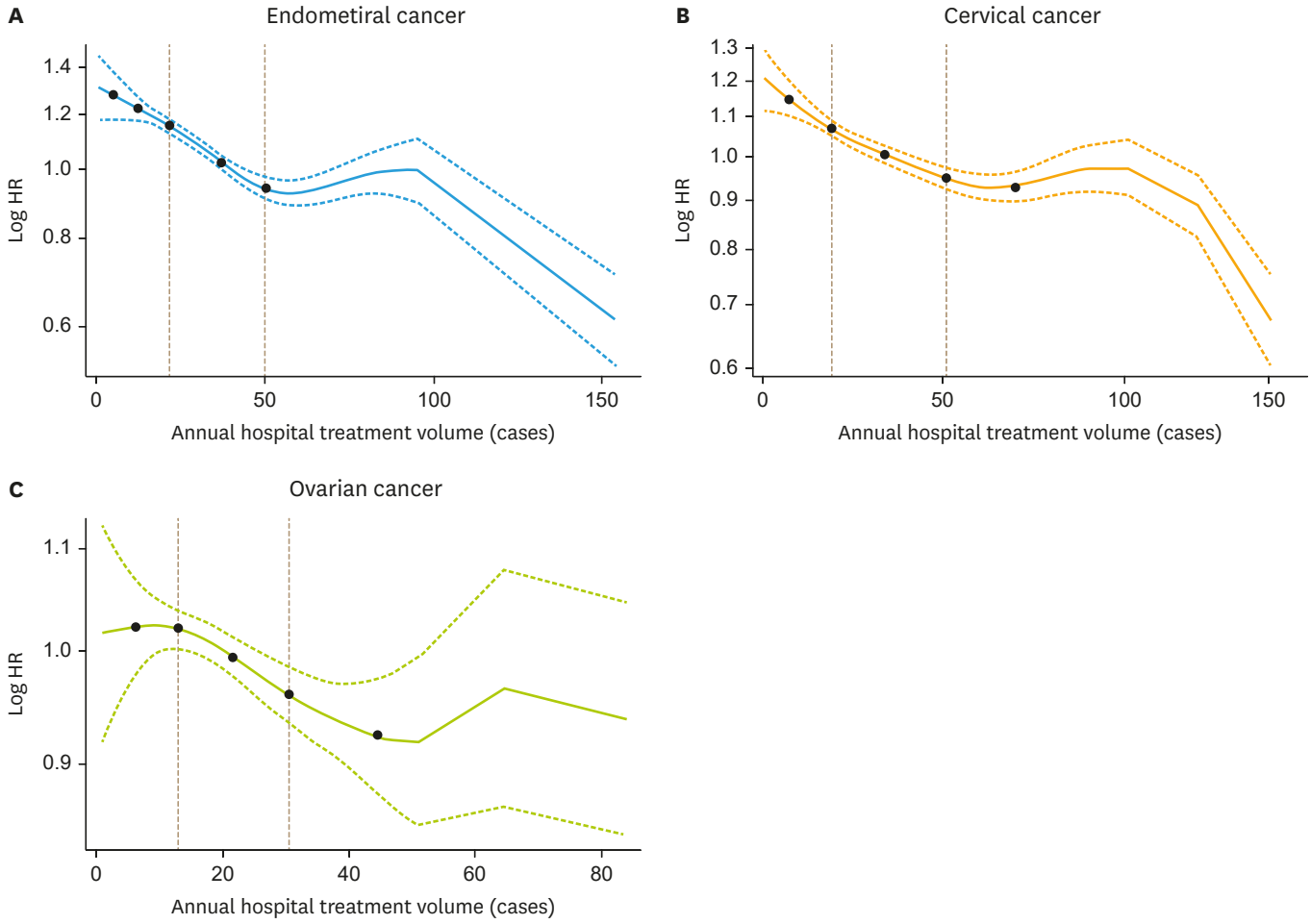

Fig. 1. Multivariable Cox proportional hazards model with restricted cubic splines. (A) Endometrial cancer, (B) Cervical cancer, and (C) Ovarian cancer. Scatter plot of log HR by average hospital treatment volume with restricted cubic spline fit. The solid line represents the RCS fit. The dotted line represents the 95% confidence interval of the RCS fit. Based on 5 knots, cut-off points are determined in the 50th and 95th percentiles for endometrial cancer, and in the 50th and 72.5th percentiles for cervical and ovarian cancers.
HR, hazard ratio; RCS, restricted cubic spline.

endometrial, cervical, and ovarian tumors, respectively); moderate- (20–49, 20–50, and 17–26 cases/year); and low-volume centers (≤19, ≤19, and ≤16 cases/year).

5. Statistical analysis

Continuous variables were assessed using one-way analysis of variance test or Kruskal-Wallis H-test. Ordinal and categorical variables were analyzed using χ^2 test. The Joinpoint Regression Program 4.8.0.1 was used to determine potential changes in temporal trends in the proportion of each group for every calendar year [16]. Additionally, a binary logistic regression model was fitted to identify independent clinicopathological factors associated with high-volume centers. Patient age, registry area, year at diagnosis, FIGO stage, tumor histology, and initial treatment data were entered into the final model, and the effect size was expressed as odds ratio (OR) with 95% confidence interval (CI). The Hosmer-Lemeshow test was used to assess the goodness of fit, and $p>0.05$, was interpreted as a good model.

Kaplan-Meier method was used to construct survival curves, and the difference between the curves was assessed using the log-rank test. To minimize bias, the available information

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was used maximally, and missing data dealt with list-wise deletion method (complete case analysis). The association between hospital treatment volume and OS was adjusted for patient age, registry area, year at diagnosis, FIGO stage, tumor histology, and initial treatment in the multivariable analysis. The Cox proportional hazard regression model was used for analysis, and the effect size is expressed as HR with 95% CI. All statistical analyses were based on a 2-sided hypothesis, with $p<0.05$ considered statistically significant. SPSS (version 26.0, IBM Corp., Armonk, NY, USA) and R statistics (version 4.0.2; R foundation for Statistical Computing, Vienna, Austria) were used for all analyses. The Reporting of studies Conducted using Observational Routinely-collected Data (RECORD) guidelines were followed in reporting the results of this observational cohort study [17].

RESULTS

1. Patient demographics

Fig. S1 shows the patient selection schema. During the study period, 223,247 women with gynecologic malignancies were included in the JSOG tumor registry. The final study population comprised 206,845 women with the 3 major invasive malignancy histological subtypes: 80,741 (39.0%), 73,647 (35.6%), and 52,457 (25.6%) women had endometrial, cervical, and ovarian tumors, respectively.

2. Demographics of high-volume centers

Tables 1-3 summarizes the patient demographics. In the 3 major types of gynecologic malignancies, all high-treatment volume centers were designated regional cancer hospitals. The majority of the women in the high-volume centers were more likely to be younger, be registered in the eastern region, be diagnosed recently, and undergone an initial surgery. In multivariable analysis, younger age, northern or eastern region, diagnosis from 2004–2007, advanced-stage endometrial and ovarian tumor, early-stage cervical tumor, and initial surgical management were identified as contributing factors for women in high-volume centers (all $p<0.05$). Per tumor histology, women in high-volume centers have rare types of tumors: type 2 endometrial and non-squamous cell cervical cancers (all $p<0.001$).

Among women underwent initial surgery (**Tables S2-S4**), lymphadenectomy was identified as a contributing factor for high-volume centers in multivariable analysis (70.8%, 73.7%, and 56.4%; adjusted-ORs: 1.20, 1.21, and 1.38 for endometrial, cervical, and ovarian tumors, respectively; all $p<0.001$). Among those with stage I diseases (**Fig. S2**), women in the high-volume centers were more likely to undergo lymphadenectomies than those in the other centers (high- [69.3%, 69.4%, and 65.1%]; moderate- [66.8%, 67.4%, and 61.0%]; and low-volume centers [62.7%, 61.0%, and 55.5%] for endometrial, cervical, and ovarian tumors, all $p<0.001$). Additionally, the number of women with endometrial and cervical tumors undergoing adjuvant therapy following the initial surgery is higher in high-volume centers than in other centers (41.4% and 41.7%; adjusted-ORs: 1.29 and 1.38 for endometrial and cervical cancers, respectively; both, $p<0.001$).

3. Hospital type-specific trends and 5-year OS rates

The temporal trends at high-volume centers were examined (**Fig. 2**). The proportion of women treated in high-volume centers decreased significantly: endometrial cancer (between 2007 and 2015: 30.5% relative decrease, annual percentage change [APC]=4.82; 95% CI=3.67–5.95; **Fig. 2A**); cervical cancer (during the study period: 13.9% relative decrease,

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Table 1. Patient demographics and contributing factor for high-treatment volume centers in endometrial tumor (n=80,741)

Characteristics	High-volume center	Moderate-volume center	Low-volume center	Adjusted OR† (95% CI)	p-value
No. of patients	15,868 (19.7)	46,350 (57.4)	18,523 (22.9)		
Annual Tx cases per Hp	67 (59–84)	32 (26–41)	14 (10–17)	-	
Designated regional cancer Hp					
Yes	15,868 (100)	40,861 (88.2)	11,351 (61.3)	-	
No	0	5,489 (11.8)	7,172 (38.7)	-	
Age (yr)	57.9±11.6	59.1±12.0	59.8±12.3		
<40	1,044 (6.6)	2,621 (5.7)	931 (5.0)	1.51 (1.39–1.65)	<0.001
40–49	2,379 (15.0)	6,744 (14.6)	2,692 (14.5)	1.31 (1.23–1.39)	<0.001
50–59	5,401 (34.0)	14,993 (32.3)	5,803 (31.3)	1.36 (1.29–1.43)	<0.001
60–69	4,495 (28.3)	12,626 (27.2)	4,922 (26.6)	1.36 (1.29–1.44)	<0.001
≥70	2,550 (16.1)	9,365 (20.2)	4,175 (22.5)	1	
Registry area					
North	1,610 (10.1)	3,890 (8.4)	1,464 (7.9)	2.20 (2.06–2.35)	<0.001
East	9,563 (60.3)	15,116 (32.6)	6,183 (33.4)	3.26 (3.13–3.40)	<0.001
Central	879 (5.5)	7,530 (16.2)	3,172 (17.1)	0.60 (0.56–0.65)	<0.001
West/south	3,816 (24.0)	19,814 (42.7)	7,704 (41.6)	1	
Year at diagnosis					
2004–2007	4,357 (27.5)	10,421 (22.5)	3,583 (19.3)	1.50 (1.43–1.57)	<0.001
2008–2011	5,222 (32.9)	15,120 (32.6)	5,098 (27.5)	1.23 (1.18–1.28)	<0.001
2012–2015	6,289 (39.6)	20,809 (44.9)	9,842 (53.1)	1	
FIGO stage					
I	10,372 (65.4)	31,338 (67.6)	13,071 (70.6)	1	
II	1,236 (7.8)	3,589 (7.7)	1,295 (7.0)	1.04 (0.97–1.10)	0.306
III	3,000 (18.9)	8,006 (17.3)	2,937 (15.9)	1.10 (1.05–1.16)	<0.001
IV	1,260 (7.9)	3,417 (7.4)	1,220 (6.6)	1.10 (1.02–1.19)	0.020
Histology					
Type 1	11,142 (70.2)	32,911 (71.0)	13,295 (71.8)	1	
Type 2	3,128 (19.7)	9,028 (19.5)	3,626 (19.6)	1.13 (1.08–1.19)	<0.001
Others	1,598 (10.1)	4,411 (9.5)	1,602 (8.6)	0.98 (0.92–1.04)	0.479
Initial treatment					
Surgery	15,152 (95.5)	43,654 (94.2)	17,449 (94.2)	1.14 (1.05–1.24)	0.001
Non-surgical management	716 (4.5)	2,696 (5.8)	1,074 (5.8)	1	
Radiation	176 (1.1)	540 (1.2)	243 (1.3)	-	
Chemotherapy	341 (2.0)	1,606 (3.5)	567 (3.1)	-	
Others	199 (1.4)	550 (1.2)	264 (1.4)	-	
Lymphadenectomy*					
Performed	10,734 (70.8)	31,152 (71.4)	11,227 (64.3)	-	
Not performed/unknown	4,418 (29.2)	12,502 (28.6)	6,222 (35.7)	-	
Adjuvant therapy*					
Performed	6,275 (41.4)	18,229 (41.8)	6,801 (39.0)		
Chemotherapy	6,074 (40.1)	17,305 (39.6)	6,525 (37.4)	-	
Radiation	201 (1.3)	924 (2.1)	276 (1.6)	-	
Not performed/unknown	8,877 (58.6)	25,425 (58.2)	10,648 (61.0)	-	

Number (%), mean±standard deviation, or median (interquartile range) are shown.
AC, adenocarcinoma; CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; Hp, hospital; OR, odds ratio; Tx, treatment.
*Among initial treatments of surgical cases (n=76,255). †Binary logistic regression model for multivariate analysis were performed to identify the independent factors for the high-volume centers. Designated regional cancer hospital was excluded due to the multicollinearity.

APC=1.85; 95% CI=1.23–2.47, **Fig. 2B**); and ovarian cancer (between 2008 and 2015: 23.4% relative decrease, APC=3.75; 95% CI=3.02–4.48, **Fig. 2C**, p<0.001). In contrast, the proportion of women in the low-volume centers increase significantly for all 3 malignancies (all, p<0.001). However, there was no significant difference in the 5-year OS rates between 2004 and 2013 in each center for the 3 malignancy types, except a significant increase in survival rates among women with cervical tumor in low-volume centers (8.2% relative increase, p=0.011; **Fig. S3**).

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Table 2. Patient demographics and contributing factor for high-treatment volume centers in cervical tumor (n=73,647)

Characteristics	High-volume center	Moderate-volume center	Low-volume center	Adjusted OR† (95% CI)	p-value
No. of patients	21,069 (28.6)	32,141 (43.6)	20,437 (27.7)		
Annual Tx cases per Hp	67 (59–91)	33 (25–41)	14 (9–18)	-	
Designated regional cancer Hp					
Yes	21,069 (100)	28,952 (90.1)	14,010 (68.6)	-	
No	0	3,189 (9.9)	6,427 (31.4)	-	
Age (yr)	51.3±15.0	53.1±15.4	53.5±15.8		
<40	5,430 (25.8)	7,222 (22.5)	4,415 (21.6)	1.70 (1.60–1.80)	<0.001
40–49	5,170 (24.5)	7,640 (23.8)	4,983 (24.4)	1.46 (1.37–1.54)	<0.001
50–59	4,061 (19.3)	6,048 (18.8)	3,765 (18.4)	1.44 (1.36–1.53)	<0.001
60–69	3,482 (16.5)	5,717 (17.8)	3,508 (17.2)	1.29 (1.22–1.37)	<0.001
≥70	2,926 (13.9)	5,514 (17.2)	3,766 (18.4)	1	
Registry area					
North	1,988 (9.8)	9,945 (30.9)	1,464 (7.9)	2.20 (2.06–2.35)	<0.001
East	9,733 (46.2)	1,512 (4.7)	1,699 (8.3)	3.26 (3.13–3.40)	<0.001
Central	1,215 (5.8)	6,213 (19.3)	3,401 (16.6)	0.60 (0.56–0.65)	<0.001
West/south	8,133 (38.6)	14,471 (45.0)	8,543 (41.8)	1	
Year at diagnosis					
2004–2007	6,129 (29.1)	8,484 (26.4)	5,294 (25.9)	1.50 (1.43–1.57)	<0.001
2008–2011	7,120 (33.8)	11,198 (34.8)	6,171 (30.2)	1.23 (1.18–1.28)	<0.001
2012–2015	7,820 (37.1)	12,459 (38.8)	8,972 (43.9)	1	
FIGO stage					
I	11,735 (55.7)	17,108 (53.2)	11,828 (57.9)	1.39 (1.30–1.49)	<0.001
II	4,710 (22.4)	7,748 (24.1)	4,509 (22.1)	1.23 (1.15–1.31)	<0.001
III	2,781 (13.2)	4,082 (12.7)	2,131 (10.4)	1.24 (1.15–1.33)	<0.001
IV	1,843 (8.7)	3,203 (10.0)	1,969 (9.6)	1	
Histology					
SCC	15,378 (73.0)	23,769 (74.0)	15,504 (75.9)	1	
AC	3,944 (18.7)	6,083 (18.9)	3,740 (18.3)	1.07 (1.02–1.11)	0.003
Others	1,747 (8.3)	2,289 (7.1)	1,193 (5.8)	1.27 (1.19–1.34)	<0.001
Initial treatment					
Surgery	13,823 (65.6)	19,480 (60.6)	12,884 (63.0)	1.48 (1.41–1.56)	<0.001
Non-surgical management	7,246 (34.4)	12,661 (39.4)	7,553 (37.0)	1	
Radiation‡	6,079 (28.9)	10,414 (32.4)	6,212 (30.4)	-	
Chemotherapy	1,103 (5.2)	2,064 (6.4)	1,156 (5.7)	-	
Others	64 (0.3)	183 (0.6)	185 (0.9)	-	
Lymphadenectomy*					
Performed	10,193 (73.7)	13,728 (70.5)	8,285 (64.3)	-	
Not performed/unknown	3,630 (26.3)	5,752 (29.5)	4,509 (35.7)	-	
Adjuvant therapy*					
Performed	5,766 (41.7)	8,354 (42.9)	4,554 (35.3)		
Chemotherapy	2,620 (19.0)	3,929 (20.2)	2,186 (17.0)	-	
Radiation‡	3,146 (22.7)	4,425 (22.7)	2,368 (18.3)	-	
Not performed/unknown	8,057 (58.3)	11,126 (57.1)	8,330 (64.7)	-	

Number (%), mean±standard deviation, or median (interquartile range) are shown.
AC, adenocarcinoma; CCRT, concurrent chemoradiotherapy; CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; Hp, hospital; OR, odds ratio; RT, radiation therapy; SCC, squamous cell carcinoma; Tx, treatment.
*Among initial treatments of surgical cases (n=4,6187). †Binary logistic regression model for multivariate analysis were performed to identify the independent factors for the high-volume centers. Designated regional cancer hospital was excluded due to the multicollinearity. ‡Including CCRT and RT only cases.

4. OS for each cancer type

Survival analyses were performed for 187,439 women. The median follow-up time was 4.73 (interquartile range [IQR]=3.13–5.54) years. The median follow-up time for 3 centers were as follows: high-volume center 5.02 (IQR=3.20–5.53), moderate-volume centers 4.75 (IQR=3.10–5.57), and low-volume centers 4.18 (IQR=3.04–5.50) years. There were 38,206 all-cause deaths and 149,233 censored cases during follow-up.

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Table 3. Patient demographics and contributing factor for high-treatment volume centers in ovarian tumor (n=52,457)

Characteristics	High-volume center	Moderate-volume center	Low-volume center	Adjusted-OR‡ (95% CI)	p-value
No. of patients	15,381 (29.3)	23,031 (43.9)	14,045 (26.8)		
Annual Tx cases per Hp	35 (31–41)	20 (17–22)	10 (8–12)	-	
Designated regional cancer Hp					
Yes	15,381 (100)	19,591 (85.1)	8,525 (60.7)	-	
No	0	3,440 (14.9)	5,520 (39.3)	-	
Age (yr)	55.9±12.9	56.5±13.4	57.4±13.6		
<40	1,567 (10.2)	2,313 (10.0)	1,305 (9.3)	1.31 (1.21–1.42)	<0.001
40–49	3,128 (20.3)	4,387 (19.0)	2,612 (18.6)	1.31 (1.22–1.40)	<0.001
50–59	4,511 (29.3)	6,498 (28.2)	3,678 (26.2)	1.29 (1.21–1.37)	<0.001
60–69	3,926 (25.5)	5,918 (25.7)	3,709 (26.4)	1.19 (1.12–1.26)	<0.001
≥70	2,249 (14.6)	3,915 (17.0)	2,741 (19.5)	1	
Registry area					
North	1,219 (7.9)	2,529 (11.0)	851 (6.1)	1.75 (1.62–1.89)	<0.001
East	9,262 (60.2)	7,484 (32.5)	4,396 (31.3)	3.75 (3.58–3.93)	<0.001
Central	1,577 (10.3)	3,581 (15.5)	2,346 (16.7)	1.30 (1.21–1.39)	<0.001
West/south	3,323 (21.6)	9,437 (41.0)	6,452 (45.9)	1	
Year at diagnosis					
2004–2007	4,020 (26.1)	5,286 (23.0)	3,124 (22.2)	1.34 (1.27–1.40)	<0.001
2008–2011	5,192 (33.8)	7,502 (32.6)	4,060 (28.9)	1.26 (1.21–1.32)	<0.001
2012–2015	6,169 (40.1)	10,243 (44.5)	6,861 (48.9)	1	
FIGO stage					
I	6,307 (41.0)	9,822 (42.6)	6,140 (43.7)	1	
II	1,504 (9.8)	2,099 (9.1)	1,319 (9.4)	1.13 (1.07–1.23)	<0.001
III	4,586 (29.8)	6,831 (29.7)	4,276 (30.4)	1.06 (1.01–1.12)	0.028
IV	1,459 (9.5)	2,081 (9.0)	1,267 (9.0)	1.12 (1.04–1.21)	0.005
NOS*	1,525 (9.9)	2,189 (9.5)	1,043 (7.4)	1.12 (0.99–1.25)	0.068
Histology					
Serous	5,478 (35.6)	8,044 (34.9)	5,030 (35.8)	1	
Non-Serous	7,761 (50.5)	11,859 (51.5)	7,066 (50.3)	0.95 (0.90–1.00)	0.051
Others	2,142 (13.9)	3,128 (13.6)	1,949 (13.9)	0.96 (0.90–1.02)	0.155
Initial treatment					
Surgery	13,345 (86.8)	20,209 (87.7)	11,646 (82.9)	1.13 (1.03–1.25)	0.014
Non-surgical management	2,036 (13.2)	2,822 (12.3)	2,399 (17.1)	1	
Chemotherapy	2,034 (13.2)	2,817 (12.2)	2,396 (9.9)	-	
Others	2 (0.0)	5 (0.1)	3 (0.0)	-	
Lymphadenectomy†					
Performed	7,529 (56.4)	10,511 (52.0)	5,319 (45.6)	-	
Not performed/unknown	5,816 (43.6)	9,698 (48.0)	6,327 (54.4)	-	
Adjuvant therapy†					
Performed	10,445 (78.3)	15,657 (77.5)	8,749 (75.1)		
Chemotherapy	10,438 (78.2)	15,633 (77.4)	8,741 (75.0)	-	
Radiation	7 (0.1)	24 (0.1)	8 (0.1)	-	
Not performed/unknown	2,900 (21.7)	4,552 (22.2)	2,897 (24.9)	-	

Number (%), mean±standard deviation, or median (interquartile range) are shown.
CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; Hp, hospital; NOS, not otherwise specified; OR, odds ratio; Tx, treatment.
*NOS as neoadjuvant chemotherapy cases without an initial clinical stage. Initial surgical treatment was defined as primary debulking surgery in patients with ovarian cancer. †Among initial treatments of surgical cases (n=45,200). ‡Binary logistic regression model for multivariate analysis were performed to identify the independent factors for the high-volume centers. Designated regional cancer Hp was excluded due to the multicollinearity.

In univariate analysis, women with endometrial tumor in high-volume centers had significantly higher OS rates than those in low-volume centers (5-year rates: stage I, 95.6% vs. 93.3%; stage II, 90.0% vs. 84.2%; stage III, 73.4% vs. 68.5%; and stage IV, 26.2% vs. 21.5%; all p<0.05; **Fig. S4**). The majority (93.9%) of women with endometrial tumor who underwent initial surgery (n=75,855) and those in high-volume centers had significantly higher OS rates (all stages; p<0.001; **Fig. S5**).

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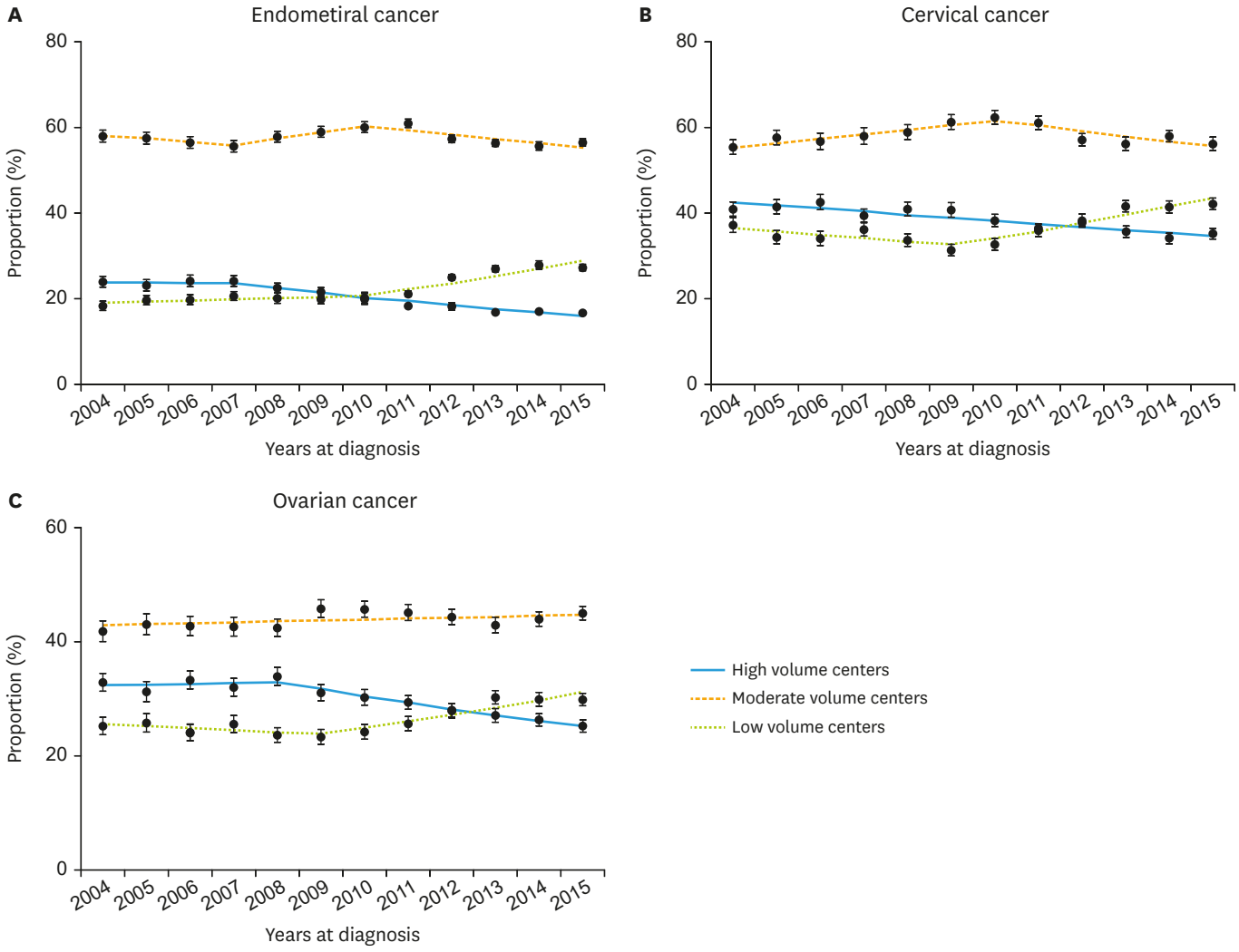

Fig. 2. Temporal trends of hospitals grouped by annual treatment volume. (A) The Y-axis is truncated to 0%–80%. (B and C) The Y-axis is truncated to 0%–60%. The annual percentage of each hospital subtype for the 3 gynecologic malignancies is shown. Lines are actual data and bars represent 95% confidence intervals. There is a significant increase in the proportion of treatments in low-volume centers since 2009 in the entire cohort, whereas the proportion of treatments in high-volume centers shows a decrease.

Women with cervical tumor in high-volume centers had significantly higher OS rates than those in low-volume centers (5-year rates: stage I, 92.3% vs. 91.6%; stage II, 76.2% vs. 70.1%; stage III, 58.4% vs. 48.0%; and stage IV, 27.8% vs. 23.0%, all p<0.05, **Fig. S4**). In terms of the survival of women who underwent initial surgery (n=46,187) and radiotherapy (n=22,705), women in high-volume centers had significantly higher OS rates than those in low-volume centers (5-year rates: stage IB with surgery, 91.5% vs. 89.7%, p=0.009; stage IB with radiotherapy, 80.4% vs. 73.1%, p=0.016; stage II with surgery, 78.8% vs. 74.0%, p=0.047; stage II with radiotherapy, 74.5% vs. 65.0%, p<0.001; **Fig. S6**).

Women with ovarian tumor in high-volume centers had significantly higher OS rates than those in low-volume centers (5-year rates: stage I, 90.0% vs. 88.5%; stage II, 76.5% vs. 73.5%; and stage III, 45.2% vs. 41.2%, all p<0.05, **Fig. S4**). Those with stage IV disease have similar OS rates (31.8% vs. 27.3%, p=0.223). The survival was also assessed in women with primary debulking surgery (PDS) (n=45,200) and neoadjuvant chemotherapy (NACT) (n=6,247).

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Table 4. Multivariate analysis of OS for 3 types of gynecologic malignancy (n=206,845)

Characteristic	Endometrial			Cervix			Ovary		
	Survival (%)	Adjusted HR† (95% CI)	p-value	Survival (%)	Adjusted HR† (95% CI)	p-value	Survival (%)	Adjusted HR† (95% CI)	p-value
Age (yr)									
< 40	93.9	1		87.1	1		80.6	1	
40–49	92.1	1.24 (1.07–1.44)	0.004	81.7	0.99 (0.93–1.05)	0.790	71.7	1.20 (1.11–1.31)	<0.001
50–59	89.0	1.51 (1.31–1.73)	<0.001	74.7	0.93 (0.87–0.98)	0.019	66.1	1.36 (1.26–1.47)	<0.001
60–69	82.2	2.12 (1.85–2.43)	<0.001	74.3	0.85 (0.80–0.90)	<0.001	59.3	1.46 (1.35–1.58)	<0.001
≥ 70	70.8	3.60 (3.14–4.12)	<0.001	62.1	1.21 (1.14–1.29)	<0.001	47.1	2.03 (1.88–2.20)	<0.001
Registry area									
North	84.5	0.94 (0.87–1.02)	0.119	76.9	1.14 (0.97–1.23)	0.558	63.5	0.97 (0.91–1.03)	0.256
East	84.5	1		76.6	1		63.1	1	
Central	84.7	0.95 (0.89–1.01)	0.101	76.7	1.03 (0.98–1.09)	0.289	64.4	0.95 (0.91–1.00)	0.051
West/south	84.4	0.96 (0.91–1.00)	0.058	77.3	1.00 (0.97–1.04)	0.870	64.6	0.92 (0.88–0.95)	<0.001
Hospital type									
High-volume	85.2	0.83 (0.78–0.88)	<0.001	79.1	0.78 (0.75–0.83)	<0.001	64.1	0.90 (0.86–0.95)	<0.001
Moderate-volume	84.4	0.94 (0.90–0.99)	0.002	75.9	0.88 (0.85–0.92)	<0.001	63.8	0.97 (0.93–1.01)	0.101
Low-volume	84.0	1		75.2	1		63.6	1	
Year at diagnosis									
2004–2007	84.8	1		75.7	1		63.1	1	
2008–2011	83.8	0.98 (0.93–1.03)	0.403	76.9	0.94 (0.90–0.98)	0.006	63.1	1.00 (0.96–1.05)	0.858
2012–2015	85.1	0.98 (0.93–1.03)	0.478	77.9	0.84 (0.80–0.88)	<0.001	65.0	0.90 (0.86–0.94)	<0.001
FIGO stage									
I	93.7	1		91.6	1		89.2	1	
II	87.7	1.84 (1.68–2.02)	<0.001	73.7	2.86 (2.70–3.03)	<0.001	75.5	2.48 (2.29–2.69)	<0.001
III	71.7	4.23 (4.01–4.47)	<0.001	53.3	4.98 (4.66–5.33)	<0.001	43.3	7.72 (7.31–8.17)	<0.001
IV	24.8	12.04 (11.35–12.78)	<0.001	25.9	11.53 (10.81–12.30)	<0.001	29.0	11.91 (11.16–12.71)	<0.001
NOS*	-	-		-	-		35.9	8.11 (7.43–8.85)	<0.001
Histology*									
Type 1/SCC/serous	92.5	1		78.6	1		49.0	1	
Type 2/AC/other AC	67.8	2.34 (2.23–2.47)	<0.001	74.3	2.04 (1.95–2.13)	<0.001	75.7	1.31 (1.26–1.37)	<0.001
Others	59.4	3.30 (3.13–3.48)	<0.001	67.3	2.27 (2.15–2.40)	<0.001	58.7	1.47 (1.40–1.54)	<0.001
Initial treatment									
Surgery	86.9	1		88.9	1		67.8	1	
Others	44.6	1.96 (1.85–2.06)	<0.001	55.9	1.96 (1.86–2.07)	<0.001	34.5	1.12 (1.05–1.19)	0.001

Five-year OS rate (%) is shown.
AC, adenocarcinoma; CI, confidence interval; HR, hazard ratio; NOS, not otherwise specified; OS, overall survival; SCC, squamous cell carcinoma.
*Histology types are listed in order of endometrial cancer, cervical cancer, and ovarian cancer. †Cox regression model for multivariate analysis.

Women who underwent PDS in high-volume centers had significantly higher OS rates than those in low-volume centers (5-year OS rates: 68.7% vs. 66.6%, p=0.001). However, the 5-year OS rates for NACT cases were similar across the 3 centers (p=0.676).

In multivariable analysis of OS (**Table 4**), older age, advanced cancer stage, rare tumor histology, and non-surgical management at initial treatment were independent contributing factors associated with decreased OS for the 3 types of malignancies. High-volume centers remain an independent prognostic factor for improved OS among women for the 3 tumor types (aHR=0.83, 0.78, and 0.90 for endometrial, cervical, and ovarian tumors, all p<0.001). Among the women who underwent initial surgery (**Table S5**), the magnitude of statistical significance for the association between treatment in high-volume centers and OS is similar for the 3 tumor types (aHR=0.82, 0.86, and 0.89 for endometrial, cervical, and ovarian tumors, all p<0.001). High-volume centers remain an independent prognostic factor for improved OS among women with cervical tumor who underwent initial radiotherapy (aHR=0.76, p<0.001; **Table S6**).

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DISCUSSION

Our findings suggest that the hospital treatment volume is highly associated with survival and clearly demonstrate that treatment at high-volume centers is associated with survival benefits among women in Japan with the 3 types of gynecologic malignancy. Adherence to best practice recommended by the JSOG guideline, such as nodal evaluation at initial surgery and delivery of postoperative adjuvant therapy, is more likely observed at high-volume centers than at low- and moderate-volume centers. However, the relative proportion of women treated at high-volume centers has recently been decreasing.

Comprehensive primary treatments of gynecologic cancer, including surgery, radiotherapy, chemotherapy, and immunotherapy, are crucial for good patient outcomes. In Japan, the numbers of comprehensive cancer centers, gynecologic oncologists, surgeons, and radiologists differ by geographic location. Moreover, a majority of specialists in cancer treatments belong to comprehensive centers and academic hospitals [18,19]. The discrepancy of distribution for medical centers and specialists could be associated with survival outcomes. Most high-volume centers investigated in this study are located in eastern Japan, especially in urban areas. The majority of women treated at these centers are young and had undergone surgical management, reflecting survival advantages due to high mobility to access medical centers and low comorbidity risks.

Additionally, surgeon's experience and surgical treatment volume are reportedly associated with improved survival and decreased risk of adverse events in several cancers [20-22]. The improved survival in high-volume centers in this study may reflect the surgical treatment volume effect. Similarly, in the high-volume centers investigated in this study, improved survival is observed for patients with cervical cancer treated with radiotherapy, including concurrent chemoradiotherapy (CCRT). Since initial radiotherapy is technically demanding and requires specialized expertise in planning and implementation, this treatment volume effect on radiotherapy confers a strong rationale. A recent randomized study reported improved survival for patients with non-small lung cancer treated with CCRT in high-volume centers [23].

Prior studies suggest that the use of evidence-based treatments and guideline adherence are associated with improved survival in patients with gynecologic cancer [24,25]. The JSOG guideline recommends that hysterectomy with/without bilateral salpingo-oophorectomy and nodal evaluation is the standard surgery for stage I gynecologic cancers, and that adjuvant therapy should be considered for cases with a high recurrence risk [26,27]. In this study, the proportion of nodal evaluation for stage I disease and postoperative adjuvant treatment were higher at high-volume centers than at other centers. The detection of potential nodal metastasis and appropriate postoperative adjuvant treatment could be responsible for the improved survival outcomes at high-volume centers.

Survival among women with ovarian cancer receiving NACT followed by surgery is similar across the 3 centers. Recent randomized studies demonstrate the non-inferiority of survival following treatment of advanced epithelial ovarian cancer with NACT compared with the standard treatment with PDS [28,29]. Thus, the utility of NACT is steadily increasing in Japan [10]. Advanced ovarian cancer demonstrates histological heterogeneity and various histological features [30]. Therefore, patients with advanced ovarian cancer cannot be treated with surgery alone. The treatment volume effect may not have impacted survival among women with ovarian cancer receiving NACT.

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Recently, the practice patterns for gynecologic malignancy in Japan have gradually shifted with the scattering of patients and decreasing number of cases in high-volume centers. This may be associated with an increase in the number of registrations in JSOG centers and an increase in the number of minimally invasive surgeries (MIS). MIS, including laparoscopic or robot-assisted hysterectomy, offers many perioperative benefits over conventional laparotomy. MIS has gained popularity as a replacement for conventional total abdominal hysterectomy at various centers [31]. MIS has been advocated as a feasible approach for managing endometrial cancer [32,33]. An on-going study examining the survival outcomes and hospital treatment volumes among women with endometrial cancer undergoing MIS is planning to validate the results of the present study.

The study strengths include a large number of cases, which reduces the risk of type II errors. While the JSOG database is extremely valuable for clinical cancer research, several limitations should be considered when interpreting results from a JSOG observational study. Many limitations involve underreported and incomplete data regarding reporting reliability, unrecorded variables, variations in data reporting, migration of patients out of the registry hospital, and selection bias. Therefore, the JSOG is improving data quality by performing rigorous quality controls by registries hospital physicians, and various data assessments have been undergoing by the committees of the JSOG [10,34-35]. Additionally, the JSOG database does not capture all newly diagnosed gynecologic malignancies in Japan. There may be discrepancies between those included in the database and those that are not.

The most notable study limitation is that assessing the volume-outcome relationship relates to the lack of definitive standard around what constitutes low-to-high volumes in gynecologic cancer cases. In this study, the data distribution to define hospital treatment volume groups was based on their relationship to survival using prior methods reported for other cancer types [22,36]. This is a retrospective study; therefore, there may be confounding factors affecting the results. For instance, information regarding cancer recurrence; patient comorbidities such as diabetes, stroke, organ failure and infection; socioeconomic backgrounds, such as incomes, last education, and insurance; and hospital-specific conditions were unavailable for analysis. The capacity of hospitals (number of beds; number of gynecologic oncologists and professional staffs with high quality of clinical experience; availability of facilities, such as operating rooms, intensive care units, and facilities for investigational modalities) is likely to be high in high-volume centers, which may result in better treatment results. These factors are strongly associated with disease morbidity and mortality. This study showed that a stratification of hospitals in Japan, according to their capability to manage the 3 major types of gynecologic malignancies, may reduce bias due to hospital capability.

These findings suggest that treatment at high-volume centers is an independent predictor of improved survival and treatment as low-volume centers requires amelioration and formulation of a new treatment strategy. To increase the level of gynecologic cancer care in Japan and improve treatment disparities, it is important to expand cooperation with high-volume centers and local hospitals or clinics, promote guideline adherence for gynecologic malignancies, train healthcare specialists and providers, and actively disseminate information on new treatments. High-volume centers could become centralized centers for evidence-based cancer treatment.

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SUPPLEMENTARY MATERIALS

Table S1
Choosing number and position of knots

Click here to view

Table S2
Patient demographics and contributing factor for high-treatment volume centers in endometrial tumor with initial surgery (n=76,255)

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Table S3
Patient demographics and contributing factor for high-treatment volume centers in cervical tumor with initial surgery (n=46,187)

Click here to view

Table S4
Patient demographics and contributing factor for high-treatment volume centers in ovarian tumor with initial surgery (n=45,200)

Click here to view

Table S5
Multivariate analysis for gynecologic cancer with initial surgery (n=168,642)

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Table S6
Multivariate analysis for cervical cancer with initial radiotherapy

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Fig. S1
Schema.

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Fig. S2
Trend of 5-year survival stratified by hospital treatment volume.

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Fig. S3
Nodal evaluation related to hospital treatment volume for stage I disease (initial surgical cohort).

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Fig. S4
OS related to hospital treatment volume for gynecologic malignancy.

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Fig. S5
OS related to hospital treatment volume for endometrial cancer (initial surgical cohort).

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Fig. S6
OS related to hospital treatment volume for cervical cancer (treatments cohort).

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