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The trend and outcome of postsurgical therapy for high-risk early-stage cervical cancer with lymph node metastasis in Japan: a report from the Japan Society of Gynecologic Oncology (JSGO) guidelines evaluation committee

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ABSTRACT

Objective: The Japan Society of Gynecologic Oncology published the first guidelines for the treatment of cervical cancer in 2007. The aim of this research was to evaluate the influence of the introduction of the first guideline on clinical trends and outcomes of patients with early-stage cervical cancer who underwent surgery.

Methods: This analysis included 9,756 patients who were diagnosed based on the pathological Tumor-Node-Metastasis (pTNM) classification (i.e., pT1b1, pT1b2, pT2b and pN0, pN1, pNX) and received surgery as a primary treatment between 2004 and 2009. Data of these patients were retrospectively reviewed, and clinicopathological trends were assessed. The influence of the introduction of the guideline on survival was determined by using a competing risk model.

Results: For surgery cases, the estimated subdistribution hazard ratio (HR) by the competing risk model for the influence of the guideline adjusted for age, year of registration, pT classification, pN classification, histological type, and treatment methods was 1.024 (p=0.864). Following the introduction of the first guideline in 2007, for patients with lymph node metastasis, the use of chemotherapy (CT) as a postsurgical therapy increased, whereas that of concurrent chemoradiotherapy (CCRT)/radiotherapy (RT) decreased (p<0.010). For pN1 cases, the estimated subdistribution HR by the competing risk model for the influence of the guideline was 1.094 (p=0.634). There was no significance in the postsurgical therapy between CT and CCRT/RT (p=0.078).

Conclusions: Survival of surgical cases was not improved by the introduction of the guidelines. It is necessary to consider more effective postsurgical therapy for high-risk early-stage cervical cancer.

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Conflict of Interest

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

Author Contributions

Conceptualization: I.M., S.M., S.S., N.S., T.F., Y.W., K.H., Y.N., A.D., M.M.; Data curation: I.M., T.F.; Formal analysis: I.M., S.M., T.F.; Funding acquisition: I.M.; Investigation: I.M., N.S., T.F., M.M.; Methodology: I.M., S.M., S.S., N.S., T.F., Y.W., K.H., Y.N., A.D., M.M.; Project administration: M.M.; Resources: I.M., T.F.; Software: I.M., T.F.; Supervision: M.M.; Validation: I.M., T.F.; Visualization: I.M., T.F.; Writing - original draft: I.M.; Writing - review & editing: I.M., S.M., S.S., N.S., T.F., Y.W., K.H., Y.N., A.D., M.M.

Keywords: Guideline Evaluation; Cervical Cancer; Surgery; Lymph Node Metastasis; Postsurgical Adjuvant Therapy

INTRODUCTION

According to the Patient Annual Report for 2017, 7,710 patients with cervical cancer stages I–IV were registered in the Japan Society of Obstetrics and Gynecology (JSOG) cancer registry program. The distribution of patients according to the International Federation of Gynecology and Obstetrics (FIGO) 2008 staging criteria was: 4,179 with stage I (54.2%); 1,882 with stage II (24.4%); 851 with stage III (11.0%); and 798 with stage IV (10.4%). Of those with stages I and II disease, 2,672 received surgery alone (34.7%), 1,118 received concurrent chemoradiotherapy (CCRT)/radiotherapy (RT) following surgery (14.4%), 818 received chemotherapy (CT) following surgery (10.5%), and 1,453 received any treatments without surgery (18.7%) [1].

In recent years, the age-adjusted uterine cancer incidence rates (all ages) have been increasing, and an increase in age-specific incidence rate was observed among younger age groups (20–50 years). This change mainly reflects the trend for the incidence rate of cervical cancer. For females, the age-adjusted rates of cancer-related mortality (all ages) has been decreasing since the late 1960s. However, unfortunately, the age-adjusted mortality rate related to cervical cancer has been recently increasing in Japan [2]. Additionally, the screening rate for cervical cancer is low (approximately 40%) [2], and the Japanese human papillomavirus vaccination program is currently at a standstill, even though the etiology and onset mechanisms of cervical cancer are currently well established.

The first edition of the guideline for the treatment of uterine cervical cancer in Japan was published by the Japan Society of Gynecologic Oncology (JSGO) in 2007 [3]. The objective of this guideline was to clearly delineate the standard of care for cervical cancer in Japan and ensure equitable care for Japanese women diagnosed with this disease. The guideline was periodically revised in 2011 [4] and 2017 [5].

The aim of this research was to evaluate the influence of the introduction of the first guideline on clinical trends and outcome of patients with early-stage cervical cancer who underwent surgery (radical hysterectomy [RH] or CCRT as a primary treatment recommended in the guideline), using JSOG cancer registry program data. Its influence on the trend of the primary treatment and patient outcome was separately analyzed in detail and reported in another article [6].

MATERIALS AND METHODS

This was a retrospective, observational study using the JSOG cancer registry program data collected between 2004 and 2009.

The JSOG gynecologic cancer registry program is one of the largest registry programs on gynecologic malignant neoplasms in Japan. A total of 447 institutions are registered with the JSOG, which submits an annual report on outcomes of gynecological procedures performed in its member institutions. The annual patient and treatment report of the committee on

gynecologic oncology of the JSOG is published in the *Journal of Obstetrics and Gynaecology Research*. In the JSOG cancer registry program, age, FIGO stage classification, Tumor-Node-Metastasis (TNM) classification by Union for International Cancer Control, image findings (i.e., tumor size, parametrial involvement, bladder invasion, lymph node metastasis, and distant metastasis), postsurgical pathological TNM (pTNM) classification, histological type, date of treatment initiation, treatment methods (i.e., primary treatment, adjuvant therapy, and neoadjuvant therapy), overall survival (OS) (i.e., 3- and 5-year), etc. are investigated. These patient data of the JSOG program cover approximately 70% of the national cancer registration program which hospitals and clinics report information on the incidence of cancer to prefectural governments under the Law Concerning the Promotion of Cancer Registration. The JSOG data are the most detailed and high-quality clinical data related to Japanese gynecologic malignant neoplasms.

This analysis included 9,756 patients who underwent RH as a primary treatment between 2004 and 2009 (**Table 1**). Patients with early cervical cancer who underwent RH and diagnosed with pT1b1, pT1b2, pT2b, pN0, pN1, pNx disease were examined (**Supplementary Table 1**). Histological types were classified into squamous cell carcinoma, adenocarcinoma, and others. Postsurgical therapies were classified into surgery alone (surgery group), surgery plus CCRT/RT (CCRT/RT group), and surgery plus CT (CT group).

Patients registered prior to 2003 were excluded as the follow-up rate was approximately 30%. For patients registered between 2008 and 2009, only 3-year OS was analyzed as a Treatment Annual Report for 5-year OS was not available at the time of the analysis; the first guideline was revised in 2011 [4].

All data were adopted for epidemiological survey and clinical trend analysis. The influence of the introduction of the guideline on the OS of patients was evaluated using data reported between 2004 and 2009. The OS between 2004–2007 (median follow-up period: 62 months) and 2008–2009 (median follow-up period: 41 months) were compared using multivariable

Table 1. Characteristics of 9,756 patients who underwent surgery as a primary treatment

Characteristic	Parameters	No. of patients (%)
Year of registration	2004–2007 (before introduction)	6,152 (63.1)
	2008–2009 (after introduction)	3,604 (36.9)
Age (yr)	≤29	460 (4.7)
	30–39	2,541 (26.0)
	40–49	2,697 (27.6)
	50–59	2,123 (21.8)
	60–69	1,417 (14.5)
	≥70	518 (5.3)
pT classification	pT1b1	6,363 (65.2)
	pT1b2	1,554 (15.9)
	pT2b	1,839 (18.8)
pN classification	pN0	7,123 (73.0)
	pN1	2,120 (21.7)
	pNx	513 (5.3)
Histological type	Squamous cell carcinoma	5,906 (60.5)
	Adenocarcinoma	2,791 (28.6)
	Others	1,059 (10.9)
Adjuvant therapy	Surgery alone	4,726 (48.4)
	Surgery+adjuvant CT	1,963 (20.1)
	Surgery+adjuvant RT/CCRT	2,976 (30.5)
	Others	91 (0.9)

CCRT, concurrent chemoradiotherapy; CT, chemotherapy; RT, radiotherapy.

analysis. Year of registration, age, pT classification, pN classification, histological types, and types of postsurgical treatments were employed as independent variables. The competing risk model, described by Fine and Gray [7,8], was employed to compare patient OS. The definition of OS in this study indicates cause-specific survival representing cancer survival in the absence of other causes of death. The Fine-Gray subdistribution hazard model permits estimation of the effect of time-invariant covariates on the cumulative incidence of the event in the presence of competing risks. The analysis was performed at a statistics center established in the Clinical Research, Innovation and Education Center, Tohoku University Hospital (Sendai, Miyagi, Japan). Outcome was analyzed using the SAS® version 9.4 (SAS Institute, Cary, NC, USA) software, while other statistical analyses were performed using the SAS® version 9.4 or JMP® Pro 12.2.0 (SAS Institute) software. The Cochran–Armitage trend test was adopted for all the trend tests. The p-values <0.05 denoted statistically significant differences. For the standardized residual analysis, an absolute value >1.96 was set as a cut-off point to assess statistically significant differences.

This study protocol was approved by the Tokai University institutional review board (IRB approval number: 13R-199). The requirement for informed consent was waived considering the retrospective nature of the study.

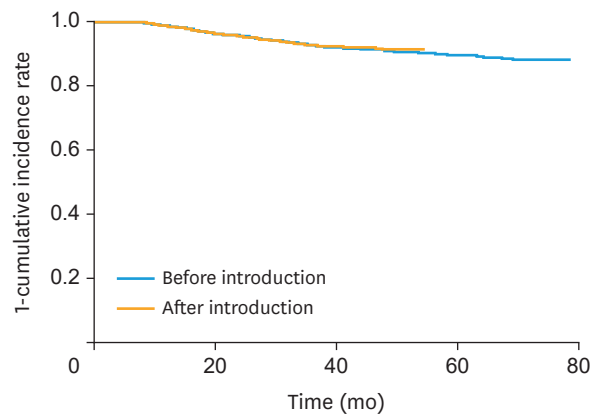
RESULTS

A total of 9,756 patients were underwent RH as a primary treatment between 2004 and 2009, and diagnosed with pT1b1, pT1b2, pT2b and pN0, pN1, pNX in pTNM classification. Patient characteristics are shown in **Table 1** and **Supplementary Table 1**. For all surgery cases, the estimated subdistribution hazard ratio (HR) by the competing risk model for the influence of the guideline adjusted for age, year of registration, pT classification, pN classification,

Table 2. Estimated subdistribution HR by the competing risk model for the influence of the introduction of the first guideline for all surgery cases

Parameter	Univariate analysis			Multivariate analysis			Interaction test
	HR	95% CI	p-value	HR	95% CI	p-value	p-value
2004–2007 (before introduction)	1.000 (ref.)			1.000 (ref.)			
2008–2009 (after introduction)	0.939	0.804–1.097	0.4288	1.024	0.784–1.337	0.8642	
Year of registration	0.977	0.936–1.019	0.2801	0.984	0.915–1.059	0.6714	0.109
Age	1.007	1.001–1.012	0.0185	0.997	0.991–1.003	0.3975	0.473
pT classification							0.354
pT1b1	1.000 (ref.)			1.000 (ref.)			
pT1b2	3.262	2.684–3.965	<0.0001	2.032	1.641–2.516	<0.0001	
pT2b	6.575	5.603–7.717	<0.0001	3.235	2.661–3.932	<0.0001	
pN classification							0.892
pN0	1.000 (ref.)			1.000 (ref.)			
pN1	5.076	4.401–5.853	<0.0001	2.400	2.036–2.830	<0.0001	
pNX	1.867	1.340–2.603	0.0002	2.010	1.449–2.788	<0.0001	
Histological type							0.047
SCC	1.000 (ref.)			1.000 (ref.)			
Adenocarcinoma	1.675	1.434–1.957	<0.0001	2.073	1.763–2.439	<0.0001	
Others	2.627	2.183–3.161	<0.0001	2.542	2.083–3.103	<0.0001	
Postsurgical therapy							<0.001
Surgery alone	1.000 (ref.)			1.000 (ref.)			
CT	6.603	5.335–8.173	<0.0001	2.582	2.000–3.335	<0.0001	
CCRT/RT	5.521	4.494–6.782	<0.0001	2.446	1.891–3.335	<0.0001	
Others	3.452	1.491–8.038	0.0039	2.081	0.876–4.943	0.0968	

CCRT, concurrent chemoradiotherapy; CI, confidence interval; CT, chemotherapy; HR, hazard ratio; ref., reference; RT, radiotherapy; SCC, squamous cell carcinoma.



No. at risk				
Before introduction	6,152	5,058	4,561	3,633
After introduction	3,603	2,803	2,075	

Fig. 1. The introduction of the first guideline: survival curve based on the 1-cumulative incidence rate. Black line represents before the introduction of the first guideline. Red line represents after the introduction of the first guideline.

histological type, and postsurgical therapies (i.e., surgery, CT, and CCRT/RT groups) was 1.024 (95% confidential interval [CI]=0.784–1.337; $p=0.864$) (**Table 2**). The survival curve related to the introduction of the guideline based on the 1-cumulative incidence rate is shown in **Fig. 1**. There was no significant effect by the guideline introduction. Additionally, the estimated HR of the CT group to the CCRT/RT group adjusted for other covariates was 1.056 (95% CI=0.897–1.243; $p=0.515$). There were no significant differences observed in terms of the guideline introduction and postsurgical therapies.

Next, we performed an interaction test between the guideline introduction and covariates to examine the groups that might have been influenced by the guideline induction, but the purpose of this exploratory analysis was to consider the trend after introducing the guideline and not to verify the effect of the guideline induction.

The p-values for the influence of the guideline introduction and interaction with covariates (i.e., year of registration, age, pT classification, pN classification, histological types, and postsurgical therapies) were 0.1094, 0.4725, 0.3537, 0.8917, 0.0466, and <0.0001 , respectively (**Table 2**). Heterogeneity was shown between postsurgical therapy and the influence of the guideline introduction. For all surgery cases, the estimated subdistribution HR of each postsurgical therapy by the competing risk model for the influence of the guideline introduction was 0.935 (95% CI=0.489–1.789; $p=0.839$), 0.920 (95% CI=0.622–1.362; $p=0.679$), and 1.362 (95% CI=0.876–2.120; $p=0.170$) for the surgery, CCRT/RT, and CT groups, respectively (**Table 3**). Although there was no statistical significance in each postsurgical therapy, the heterogeneity was only observed in the CT group and it was suggested that the mortality risk tended to be higher in the CT group versus the surgery or CCRT/RT groups after the introduction of the guideline.

Following the introduction of the first guideline in 2007, for pN1 cases, the proportion of the surgery group did not change; however, the proportion of the CT group as a postsurgical therapy was increased, whereas that of the CCRT/RT group was decreased ($p<0.010$) (**Fig. 2**). For pN1 cases (**Supplementary Table 2**), the estimated subdistribution HR by the competing

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Table 3. Estimated subdistribution HR of postsurgical therapy by the competing risk model for each treatment after the introduction of the first guideline

Postsurgical therapy	Parameter	HR	95% CI	p-value
Surgery alone (n=4,626)	2004–2007 (before introduction)	1.000 (ref.)		
	2008–2009 (after introduction)	0.935	0.489–1.789	0.839
	Year of registration	0.958	0.803–1.143	0.633
	Age	1.014	1.000–1.029	0.052
	pT classification			
	pT1b1	1.000 (ref.)		
	pT1b2	2.980	1.831–4.850	<0.001
	pT2b	3.869	1.850–8.093	<0.001
	pN classification			
	pN0	1.000 (ref.)		
	pN1	5.270	2.746–10.113	<0.001
	pNX	1.095	0.497–2.414	0.822
	Histological type			
	SCC	1.000 (ref.)		
	Adenocarcinoma	1.562	1.009–2.418	0.046
Others	3.405	2.098–5.527	<0.001	
CT (n=1,963)	2004–2007 (before introduction)	1.000 (ref.)		
	2008–2009 (after introduction)	1.362	0.876–2.120	0.170
	Year of registration	0.909	0.804–1.028	0.130
	Age	0.994	0.984–1.004	0.208
	pT classification			
	pT1b1	1.000 (ref.)		
	pT1b2	1.518	1.084–2.127	0.015
	pT2b	2.976	2.237–3.957	<0.001
	pN classification			
	pN0	1.000 (ref.)		
	pN1	2.831	2.181–3.675	<0.001
	pNX	4.805	2.886–7.999	<0.001
	Histological type			
	SCC	1.000 (ref.)		
	Adenocarcinoma	2.041	1.561–2.669	<0.001
Others	2.248	1.637–3.088	<0.001	
CCRT/RT (n=2,976)	2004–2007 (before introduction)	1.000 (ref.)		
	2008–2009 (after introduction)	0.920	0.622–1.362	0.679
	Year of registration	1.036	0.933–1.150	0.511
	Age	0.992	0.983–1.001	0.075
	pT classification			
	pT1b1	1.000 (ref.)		
	pT1b2	1.911	1.413–2.586	<0.001
	pT2b	2.854	2.204–3.696	<0.001
	pN classification			
	pN0	1.000 (ref.)		
	pN1	1.834	1.479–2.274	<0.001
	pNX	1.358	0.807–2.286	0.249
	Histological type			
	SCC	1.000 (ref.)		
	Adenocarcinoma	2.303	1.823–2.908	<0.001
Others	2.470	1.816–3.360	<0.001	

(continued to the next page)

risk model for the influence of the guideline adjusted for age, year of registration, pT classification, histological type, and postsurgical therapies (i.e., surgery, CT, and CCRT/RT groups) was 1.094 (95% CI=0.756–1.583; p=0.634) (**Table 4**). Additionally, the estimated HR of the CT group to the CCRT/RT group adjusted for other covariates was 1.206 (95% CI=0.979–1.486; p=0.078). This was not in agreement with the guideline, but there were no significant differences observed in terms of the guideline introduction and postsurgical therapies.

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Table 3. (Continued) Estimated subdistribution HR of postsurgical therapy by the competing risk model for each treatment after the introduction of the first guideline

Postsurgical therapy	Parameter	HR	95% CI	p-value
Others (n=91)	2004–2007 (before introduction)	1.000 (ref.)		
	2008–2009 (after introduction)	0.920	0.622–1.362	0.679
	Year of registration	1.036	0.933–1.150	0.511
	Age	0.992	0.983–1.001	0.075
	pT classification			
	pT1b1	1.000 (ref.)		
	pT1b2	1.911	1.413–2.586	<0.001
	pT2b	2.854	2.204–3.696	<0.001
	pN classification			
	pN0	1.000 (ref.)		
	pN1	1.834	1.479–2.274	<0.001
	pNX	1.358	0.807–2.286	0.249
Histological type				
SCC	1.000 (ref.)			
Adenocarcinoma	2.303	1.823–2.908	<0.001	
Others	2.470	1.816–2.908	<0.001	

CCRT, concurrent chemoradiotherapy; CI, confidence interval; CT, chemotherapy; HR, hazard ratio; ref., reference; RT, radiotherapy; SCC, squamous cell carcinoma.

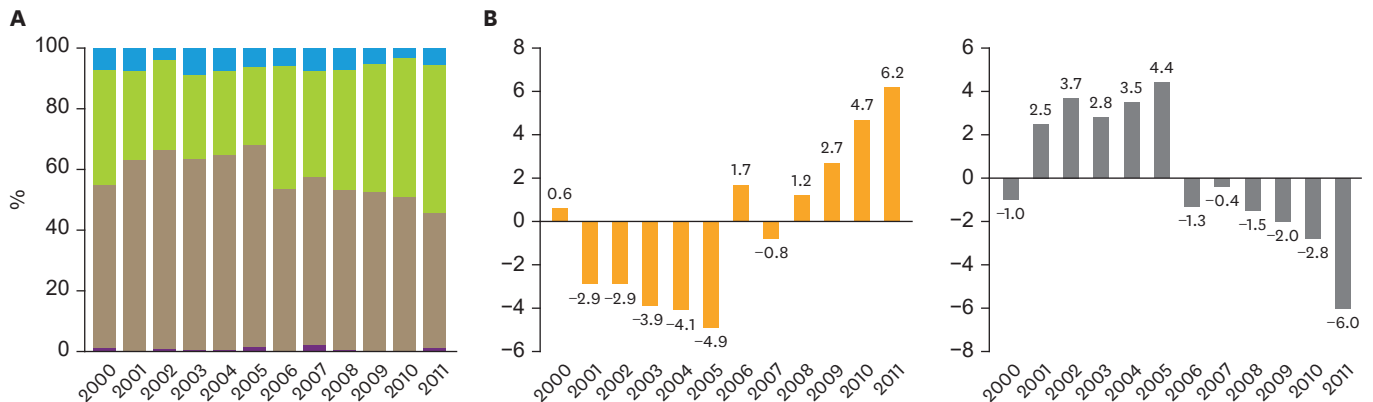


Fig. 2. (A) The trend of postsurgical therapy for pN1 cases after introducing the first guideline (Cochran–Armitage trend test). Following the introduction of the first guideline in 2007, for pN1 cases, the use of CT as a postsurgical therapy increased, whereas that of CCRT/RT decreased ($p < 0.010$). Blue represents surgery alone; Green represents adjuvant chemotherapy; Ocher represents adjuvant CCRT/RT; Purple represents others. (B) The trend of postsurgical therapy for pN1 cases after introducing the first guideline (standardized residual analysis). Orange represents adjuvant chemotherapy; Gray represents adjuvant CCRT/RT. CCRT, concurrent chemoradiotherapy; CT, chemotherapy; RT, radiotherapy.

Table 4. Estimated subdistribution HR by the competing risk model for the influence of the introduction of the first guideline for pN1 cases

Parameter	Univariate analysis			Multivariate analysis			Interaction test
	HR	95% CI	p-value	HR	95% CI	p-value	p-value
2004–2007 (before introduction)	1.000 (ref.)			1.000 (ref.)			
2008–2009 (after introduction)	0.975	0.788–1.206	0.814	1.094	0.756–1.583	0.634	
Year of registration	0.991	0.936–1.049	0.756	0.993	0.985–1.001	0.080	0.283
Age	1.001	0.993–1.009	0.790	0.960	0.869–1.061	0.426	0.862
pT classification							0.413
pT1b1	1.000 (ref.)			1.000 (ref.)			
pT1b2	1.707	1.253–2.326	<0.001	1.604	1.174–2.192	0.003	
pT2b	2.742	2.143–3.507	<0.001	2.866	2.234–3.676	<0.001	
Histological type							0.278
SCC	1.000 (ref.)			1.000 (ref.)			
Adenocarcinoma	2.334	1.892–2.878	<0.001	2.210	1.772–2.757	<0.001	
Others	2.071	1.596–2.688	<0.001	2.037	1.553–2.672	<0.001	
Postsurgical therapy							<0.001
CCRT/RT	1.000 (ref.)			1.000 (ref.)			
Surgery alone	1.136	0.774–1.735	0.553	1.172	0.761–1.805	0.472	
CT	1.470	1.211–1.784	0.001	1.206	0.979–1.486	0.078	
Others	1.656	0.685–4.007	0.263	1.978	0.766–5.107	0.159	

CCRT, concurrent chemoradiotherapy; CI, confidence interval; CT, chemotherapy; HR, hazard ratio; ref., reference; RT, radiotherapy; SCC, squamous cell carcinoma.

DISCUSSION

This was the first study to assess the influence of the introduction of the first guideline on clinical trends and outcome of patients with early-stage cervical cancer who underwent surgery by the JSGO guideline evaluation committee in Japan. The effect of this introduction was unclear based on this evaluation. Survival of surgical cases was not improved by the introduction of the guidelines. For patients with positive pelvic lymph node metastasis, CT which the usefulness was unknown, tended to be selected as a postsurgical therapy in Japan, but there were no significant differences observed in terms of the guideline introduction and the postsurgical therapies (i.e., CT and CCRT/RT groups).

The 2007 JSGO guidelines for the treatment of uterine cervical cancer state the following: (1) postsurgical adjuvant therapy is recommended for patients with positive pelvic lymph node metastasis; (2) postsurgical adjuvant therapy should be considered for patients with high-risk factors for recurrence other than positive pelvic lymph node metastases; (3) whole-pelvis irradiation is considered to be a postsurgical adjuvant therapy, and CCRT should also be considered for patients with positive lymph node metastases; and (4) presently, the usefulness of postsurgical adjuvant CT is unknown [3]. Our results demonstrated that postsurgical adjuvant CT tended to be selected for patients with positive pelvic lymph nodes metastasis (pT1b1N1, pT1b2N1, pT2bN1), although there were no certain trends observed for patients with parametrial involvement (pT2bN0) (**Supplementary Fig. 1**) or bulky tumors (pT1b2N0). This was not in agreement with the guideline regarding postsurgical therapy, recommending CCRT/RT for a high-risk group for recurrence (i.e., N1), but a significant difference was not recognized between CT group and CCRT/RT group which was widely accepted as postsurgical therapy for high-risk early-stage cervical cancer patients.

Numerous studies reported that positive pelvic lymph node metastasis, parametrial involvement, surgical margin involvement, lympho-vascular space involvement (LVSI), deep stromal invasion (DSI), and bulky tumor size are risk factors for the recurrence of early-stage cervical cancer after RH. Particularly, the presence of positive pelvic lymph node metastasis has more influence than other factors. Patients with positive pelvic lymph node metastasis are linked to increased recurrence rate of postsurgical cervical cancer ($\leq 40\%$) compared with those without this factor and a greater rate of distant failure [9-13].

There are 3 theories regarding the spread of cancer: the Halstedian theory as local disease; the Fisher theory as systemic disease with distant metastases from the outset; and the spectrum theory as heterogeneous disease with both local disease in non-invasive or microinvasive cancer and systemic disease in invasive cancer [14]. These points of views have different implications for the selection of postsurgical therapy for patients with positive pelvic lymph node metastasis.

A possible explanation for our results is that the presence of positive pelvic lymph node metastasis is considered systemic disease with microscopic tumor spread. At the time of the diagnosis of positive pelvic lymph node metastasis, systemic spread of cancer cells or micro-metastatic involvement have already occurred, and local therapy may be insufficient to improve patient survival under these conditions. Therefore, a certain proportion of Japanese gynecologic oncologists support that systemic treatment (i.e., CT) is considered more effective than local treatment (i.e., CCRT/RT) for patients with positive pelvic lymph node metastasis. These gynecologic oncologists may consider that positive pelvic lymph

node metastasis should be treated separately from other risk factors, such as parametrial involvement/surgical margin involvement/bulky tumor size without positive pelvic lymph node metastasis (pT1b1N0/pT1b2N0/pT2bN0). The estimated HR of each postsurgical therapy tended to be higher in the CT group versus the surgery or CCRT/RT groups. However, it was not possible to determine whether patient survival in the CT group was inferior to that observed in the CCRT/RT group as a postsurgical therapy was not in agreement with the guideline, because our result showed that there was no significant difference in postsurgical therapies. Positive pelvic lymph node metastasis itself is associated with poor prognosis. Presently, it is unclear whether CCRT as a postsurgical therapy improves OS in patients with positive lymph node metastases.

Peters et al. [15] reported that the addition of concurrent cisplatin-based CT to RT significantly improved progression-free survival and OS of high-risk patients who underwent RH and pelvic lymphadenectomy for early-stage cervical cancer. However, the superior survival of postsurgical CCRT versus RT in early-stage cervical cancer with positive pelvic lymph node metastasis has not been recognized. Although postsurgical RT has been used for patients with positive pelvic lymph nodes metastasis, the studies have only shown a decrease in the local failure rate and no improvement in survival [16,17]. Matsuo et al. [18] reported that there was no association between CCRT use and improved survival despite the increase in the use of postsurgical CCRT for early-stage cervical cancer with positive pelvic lymph node metastasis.

In Japan, a phase III, randomized, comparative study of postsurgical CCRT or CT following RH for patients with positive pelvic lymph node metastasis and/or parametrial involvement in stage IB–IIB, termed “Adjuvant Chemotherapy Versus Radiotherapy For Postoperative Cervical Cancer (AFTER trial) (JGOG1082)”, has been ongoing since June 2019. CCRT or CT as a postsurgical therapy will be evaluated in this clinical trial, and the result will be associated with improved OS for high-risk early-stage cervical cancer patients with positive pelvic lymph node metastasis in the field of postsurgical management.

Or when positive pelvic lymph node metastasis is linked to poorer prognosis than other factors (e.g., parametrial involvement, etc.), current postsurgical CCRT or CT for pelvic lymph node positive early-stage cervical cancer is not effective [19]. Thus, we need to develop more intensive treatment strategies for improving OS. It may be necessary to use both CCRT and CT for postsurgical adjuvant therapy to concurrently control local recurrence and prevent distant metastasis. In the USA, there is currently an ongoing phase III trial (RTOG-0724), which investigates whether administering adjuvant systemic CT after CCRT will improve disease-free survival versus CCRT alone in patients with high-risk early-stage cervical carcinoma with positive pelvic lymph nodes metastasis and/or positive parametrial involvement after RH. The results of the 2 aforementioned trials will be useful for decision-making regarding postsurgical therapy.

Another reason for the selection of CT as a postsurgical therapy for patients with positive pelvic lymph node metastasis is that lymphadenectomy is thoroughly performed in Japan. Sakuragi et al. [20] reported that metastasis to bilateral pelvic lymph nodes (excluding the common iliac lymph nodes) and metastasis to the common iliac lymph nodes were related to paraaortic lymph node metastasis. In the study, the total numbers of lymph nodes dissected per patient ranged 31–149 (mean: 67.9). The number of paraaortic lymph nodes ranged 2–32 (mean: 12.0), and the total number of pelvic lymph nodes ranged 24–117 (mean: 56.4). In

1999, Lahousen et al. [9] evaluated the effect of adjuvant therapy in patients with high-risk cervical cancer following RH; the Austrian Gynecologic Oncology Group conducted a prospective, randomized, multicenter clinical trial between 1989 and 1995 (phase III study of adjuvant CT, adjuvant RT, or observation only for high-risk patients with stage IB, IIA, or IIB cervical cancer after primary surgery). After a median follow-up of 4.1 years there were no statistically significant differences in disease-free survival among the 3 treatment arms. The data suggested that adjuvant CT or RT did not improve the survival or recurrence rates in high-risk patients with cervical cancer after RH. The most important treatment for these patients appeared to be RH with systematic pelvic lymphadenectomy without residual tumors.

RH has a long history of application in Japan and all over the world. The method was established by Ernst Wertheim as a surgical technique for the treatment of invasive cervical cancer. However, owing to the complicated anatomy of the pelvis, the method has been modified by many surgeons. Among these modifications, the Okabayashi method (published in 1921) was more radical and outstanding. Subsequently, this method became a standard surgical procedure for the treatment of invasive cervical cancer in Japan [21]. RH using the Okabayashi method yielded high cure rates and achieved pelvic local control. Surgery at centers with high volume (≥ 105 surgeries) or JSGO-accredited institutions is associated with decreased local recurrence risk and improved survival of patients with early-stage cervical cancer [22,23]. Consequently, CT may be selected for the prevention of distant metastasis in patients with positive pelvic lymph node metastasis. CT was associated with a decreased risk of distant recurrence and an increased risk of local recurrence versus CCRT; however, patients who received CT had similar recurrence and mortality rates compared with those who received CCRT/RT [24,25].

Additionally, RH with thorough pelvic lymphadenectomy without residual tumors is associated with increased occurrence of serious adverse events of postsurgical adjuvant CCRT/RT. The combination of these radical treatments increases the risk of complications, such as leg lymphedema and bowel obstruction, compared with either treatment alone [26]. Machida et al. [27] reported that, for clinical stages IB–IIB cervical cancer, RT-based adjuvant therapy was associated with an increased risk of postsurgical complications (RT alone, adjusted-odds ratio [OR]=3.19; $p=0.004$ and RT plus CT, adjusted-OR=3.26; $p=0.001$), whereas adjuvant CT increased the risk of bladder dysfunction (adjusted-OR=2.06; $p=0.01$). CT may be selected to reduce postsurgical complications if RH with systemic pelvic lymphadenectomy without residual tumors (i.e., completely controlled local disease) is performed by highly skilled gynecologic oncologists. The selection of postsurgical therapy is significantly affected by the completeness of RH.

Ikeda et al. [28] revealed the variety of adjuvant therapies administered among Japanese institutions for intermediate/high-risk cervical cancer after RH. RT was appropriate in case of vaginal stump invasion, CCRT was appropriate in cases of positive pelvic lymph node metastasis and parametrial invasion, and CT was widely adopted for all risk factors except vaginal stump invasion. CT following RH was effective in patients with intermediate-risk (DSI $>50\%$, bulky tumor >4 cm, and LVSI) stage IB cervical cancer [29]. At 96 of the 166 active member institutions (57.9%) of the Japanese Gynecologic Oncology Group, high-risk patients underwent CCRT after RH. On the other hand, adjuvant CT was administered to high-risk and intermediate-risk patients at 19.9% and 33.1% of the institutions, respectively. More than half of the 166 institutions considered the number of metastatic lymph nodes (91/166, 54.8%) and histological type (116/166, 69.9%) when selecting adjuvant therapy [30]. Our results

suggested that, although CCRT as a postsurgical therapy was the global standard for early-stage cervical cancer patients with positive pelvic lymph node metastasis, adjuvant therapy was selected based on the type of risk factor in Japan.

This study had several limitations to analyze in more depth. Firstly, this was a retrospective study. The presence of patient comorbidities, performance status, and postsurgical therapy decision-making processes were unknown. Secondly, institutional surgical volume (high, intermediate, low) and level of surgeons (gynecologic oncologist with license or without license, gynecologist) were unknown. Thirdly, details regarding RH, pelvic lymphadenectomy, CT, RT, CCRT, and adverse events were not available in this study. Finally, the guideline has been revised twice so far since the first guideline was published. Therefore, it is difficult to clearly evaluate the influence of the introduction of each revised edition.

In conclusion, we believe the diverse analysis offers the current situation of the treatment for early-stage cervical cancer who underwent RH in Japan. Although survival was not improved by the introduction of the first guidelines, we demonstrated its possible influence on the clinical trend of postsurgical therapy and highlighted the main issues in the future. Especially, a certain number of Japanese gynecologic oncologists selected CT as postsurgical therapy for patients with positive pelvic lymph node metastasis, and this selection was not in agreement with the guideline. In recent years, CCRT has been evaluated in Europe and the USA. However, the results of the studies are unsatisfactory with regards to improving the survival of patients with positive pelvic lymph node metastasis of early-stage cervical cancer. We keep continuous evaluation to resolve the issues identified in this research, and will develop more effective postsurgical therapies for contributing to better patient outcome.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1

Characteristics of 9,756 patients who underwent surgery as a primary treatment

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Supplementary Table 2

Characteristics of 2,120 (pN1) patients who underwent surgery as a primary treatment

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Supplementary Fig. 1

(A) The trend of postsurgical therapy for pT2b cases after introducing the first guideline (Cochran–Armitage trend test). Following the introduction of the first guideline in 2007, for pT2b cases, there was no significance difference observed in postsurgical therapies. Blue represents surgery alone; Green represents adjuvant chemotherapy; Ocher represents

adjuvant CCRT/RT; Purple represents others. (B) The trend of postsurgical therapy for pT2b cases after introducing the first guideline (standardized residual analysis). Orange represents adjuvant chemotherapy; Gray represents adjuvant CCRT/RT.

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