Retrospective analysis of prognosis using the Gynecology Oncology Group score of stage IB-IIA node negative uterine cervical cancer after radical hysterectomy and trachelectomy

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Abstract. There is currently controversy regarding the criteria for low and intermediate risk of cervical cancer (CC) after surgery. In the present study, the Gynecology Oncology Group (GOG) score was used to detect intermediate risk. Adjuvant radiotherapy was applied in the case of a GOG score >120. The present study aimed to evaluate the validity of the recurrence risk classification using the GOG score for stage IB-IIA node-negative CC. All cases of stage IB-IIA node-negative CC who underwent radical surgery between February 2007 and December 2015 were retrospectively reviewed. The GOG scores were determined from clinical and pathological findings and accordingly, subjects were divided into 4 groups: A, ≤40; B, >40 and ≤70; C, >70 and ≤120; and D, >120. Overall survival (OS) and recurrence-free survival (RFS) curves were generated using the Kaplan-Meier method. The log-rank test produced an estimated P-value by comparing the OS and RFS of group A (low-score group) with those of others. The present study included 61 patients (mean age, 47.82 years; age range, 22-76 years) and the median follow-up was 79 (39-149) months. Of these, 60 patients were observed for at least 60 months. During the follow-up period, the OS and RFS rates of group C were 94.7 and 84.2%, respectively, while those of group D were 100 and 91.7%, respectively; the OS and RFS of groups A and B were 100%. Log-rank tests for all OS and RFS indicated no significant differences compared to group A. It was indicated that a GOG score ≤70 does not require adjuvant therapy; however, a GOG score >70 requires consideration of adjuvant therapy based on the risk factors which constitute the score.

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Introduction

In Japan, uterine cervical cancer (CC) is a frequent cancer type in females, with 10,978 individuals affected in 2018. Radical hysterectomy (RH) is selected and performed in Japan, particularly for stage IB-IIA CC. Japanese CC guidelines indicate that surgery was performed as the primary treatment in 90, 79, 66 and 59% of patients with stage IB1, IB2, IIA1 and IIA2 CC, respectively (1). Based on pathological assessment after RH, gynecologists decide whether adjuvant therapy should be applied or not. To evaluate the requirement for adjuvant therapy in early-stage CC with negative pelvic nodes and negative parametrial invasion, several guidelines indicated that histopathological assessment must determine tumor size, depth of cervical stromal invasion and the presence of lymphovascular invasion as risk factors for recurrence. The National Comprehensive Cancer Network (NCCN) guidelines version 4.2019 described that if the surgical findings met the Sedlis criteria, external pelvic radiation was required (2). The British Gynaecological Cancer Society guidelines defined intermediate-risk factors as follows: i) Presence of lymphovascular space invasion; ii) tumor maximum diameter >4 cm at final pathology; and iii) deep cervical stromal invasion (3). On the other hand, the Japanese guidelines describe flexible scales of tumor volume and depth of stromal invasion and there are different criteria regarding tumor volume and depth of stromal invasion at each institution (2).

Our group has been using a prognostic risk scoring system called the Gynecologic Oncology Group (GOG) score to evaluate the risk of recurrence since 2007. This system, reported by Delgado *et al* (4) from the GOG, comprises multiplying the relative risks assigned for three factors: Tumor penetration, tumor size and lymph vascular invasion. A GOG score >120 correlated with a 41% risk of recurrence without adjuvant therapy after RH. Therefore, adjuvant therapy for patients according to this criterion is thought to be justifiable. By reference to the protocol reported by Kridelka *et al* (5), the basis of a GOG score >120 has been adopted by our group as an

adjuvant therapy criterion. In the present study, the validity of the GOG score as a basis for adjuvant therapy was evaluated in cases of stage IB-IIA node-negative CC after RH and pelvic lymphadenectomy.

Patients and methods

Patients. The present study was a retrospective analysis involving patients diagnosed with stage IB-IIA CC, according to the International Federation of Gynecology and Obstetrics (FIGO) 2008 classification, admitted to the hospital of the University of Occupational and Environmental Health (Fukuoka, Japan) between February 2007 and December 2015. The exclusion criteria were as follows: Presence of lymph node metastasis, positive surgical margin and parametrial invasion from postoperative pathological findings; or the patient received therapies other than radical surgery as the primary therapy. The medical ethics committee of the University of Occupational and Environmental Health (Fukuoka, Japan) approved the present study (reference no. H30-160) and an opt-out policy was provided on the web. The present study was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki.

Surgery. To determine the FIGO staging, magnetic resonance imaging (MRI), computed tomography (CT) and pelvic examination under anesthesia were performed. All patients were treated with type C radical surgery and pelvic lymphadenectomy (6). Operations were performed under the supervision of gynecologic oncologists certified by the Japan Society of Gynecologic Oncology.

GOG scoring. The requirement for adjuvant therapy was determined by the GOG score according to preoperative imaging examination and histopathological findings. The tumor diameter was evaluated by vaginal speculum examination, preoperative MRI based on the interpretation of a radiologist and histopathological examination of the conization specimen. The depth of tumor stromal invasion and capillary/lymphatic space invasion were evaluated using histopathological examination performed by two or more pathologists. Based on the histopathological reports from the pathology department, the scoring system according to the original paper by Delgado *et al* (4) was calculated in a weekly gynecologic cancer board. The score was calculated by multiplying the relative risks assigned for the 3 factors according to Delgado's original paper, which are the tumor size, depth of invasion (DOI) and lymph vascular space invasion (LVSI). Adjuvant therapy with radiotherapy was performed in patients with a GOG score >120.

Adjuvant radiotherapy. The radiation oncologist finalized the treatment plan involving the use of radiation therapy (RT) and the gynecologist determined whether concurrent chemotherapy was to be administered, considering potential complications. Adjuvant RT started within 2-4 weeks after surgery. The clinical target volume (CTV) included the common iliac vessels, external and internal iliac vessels, presacral area, parametrium and upper vagina, according to the RT Oncology Group CTV guidelines for whole-pelvis RT (7). The total radiation dose was 50 or 50.4 Gy in 25 or 28 fractions, respectively (daily fractions of 1.8 or 2.0 Gy over 5-6 weeks, 5 fractions per week) except for 1 patient who was treated with boost irradiation to the primary tumor bed (total dose of 61.2 Gy, daily fraction of 1.8 Gy) due to dense adhesion of the primary tumor to the bladder. Unless there was a specific contraindication, concurrent chemotherapy with cisplatin (40 mg/m^2) was administered weekly.

Observation/follow-up. The patients were instructed to visit our hospital every 1-3 months for the first 1-2 years, then every 3-6 months in the 3rd year and every 6 months in the 4th and 5th years. Clinical examinations, such as PAP smear, pelvic examination and tumor marker detection, were performed at each visit and CT was performed every 6 months.

Statistical analysis. The primary endpoint of the present study was overall survival (OS) and recurrence-free survival (RFS) according to the groups stratified based on the GOG score as follows: Group A, ≤40; group B, >40 and ≤70; group C, >70 and ≤120; and group D, >120. The Kaplan-Meier method was used for survival analysis and statistical significance was determined using the log-rank test. The age differences were analyzed using Student's t-test and categorical variables were analyzed with the χ^2 test or Fisher's exact test.

All statistical analyses were performed with EZR ver 4.0.2 (Saitama Medical Center, Jichi Medical University), which is a graphical user interface for R (The R Foundation for Statistical Computing), at a significance level of $P<0.05$ (8). More precisely, it is a modified version of R commander (version 1.51) that was designed to add statistical functions frequently used in biostatistics.

Results

Patient characteristics. A total of 88 patients diagnosed with stage IB-IIA CC were identified and preliminarily enrolled based on the exclusion criteria in Fig. 1. Finally, 61 patients matched the inclusion criteria and were included in the analysis; their characteristics are presented in Table I. The patients' mean age was 47.82 years (age range, 22-76 years). The median follow-up period was 79 (range, 39-149) months, excluding one patient who was lost to follow-up at 39 months. A total of four patients had recurrence and two patients died of disease (Table II). The overall relapse rate and morbidity rate were 6.56% (four out of 61) and 3.28% (two out of 61), respectively. None of the patients had any other malignant diseases or died of intercurrent diseases.

The common decades of life of affected subjects were the forties (27.9%), thirties (24.6%) and fifties (16.4%). Unlike the population of the patients, all patients with recurrence or who died of disease were >60 years of age (4 patients). FIGO stage IB1 was the most frequent stage (50 of 61 patients; 82.0%) and four patients had recurrence. RH was performed in 59 patients and radical trachelectomy was applied in two nulliparous patients to preserve their fertility. The tumor size in the two patients who received trachelectomy was 1.6 and 2.4 cm in diameter and the pathological diagnosis was squamous cell carcinoma (SCC) in both cases. The common histological types, from most to least, were SCC

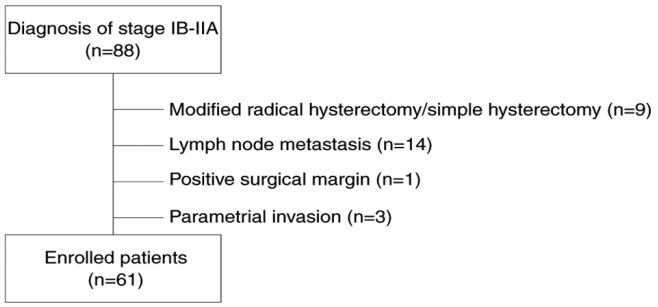

Figure 1. Flow chart of patient selection; 88 patients diagnosed with stage IB-IIA cervical cancer were identified and 61 patients met the inclusion criteria.

(36 of 61 patients; 59%), adenocarcinoma (19 of 61; 31.1%) and adenosquamous carcinoma (6 of 61; 9.8%). A total of four patients with recurrent disease were diagnosed with SCC (2 patients), adenocarcinoma (1 patient) and adenosquamous cell carcinoma (1 patient). Furthermore, two patients with SCC survived after additional therapy (radiation therapy for intrapelvic recurrence and chemotherapy with irinotecan and nedaplatin for liver metastasis) without any evidence of further malignancy during the follow-up period.

Tumor sizes of ≥3 and <4 cm (39.3%) and ≥2 and <3 cm (21.3%) were common; furthermore, all four patients with recurrence were detected in these groups and had intermediate or deep invasion and LVSI. A total of 48 patients had a GOG score ≤120. Of the 13 patients with a GOG score >120, 10 received adjuvant RT. The remaining three patients declined, with 1 preferring chemotherapy and two preferring no adjuvant treatment. Furthermore, three patients with GOG ≤120 had recurrence and one of them died of disease. All patients with recurrent disease had over one-half of stromal invasion and had LVSI.

Response and survival analysis. A total of 60 patients, except for one patient with double cancer, were analyzed using the Kaplan-Meier method and the log-rank test. In Fig. 2, OS and RFS are presented according to stratified groups by GOG score during the overall follow-up period. In both groups A and B, OS and RFS of patients involved no recurrence. By contrast, the OS of group D and the RFS of group C were both low. The log-rank test was applied to obtain P-values for comparisons of group A (GOG score; ≤40) as a low-score group with the others. The OS and RFS of both groups C and D were low; however, the log-rank test indicated no significant differences compared to group A. Table III indicates the 5-year OS rate and 5-year RFS rate according to the groups. As one patient in group D died of disease after five years of primary treatment, this case did not reflect the 5-year OS of group D. In total, the 5-year OS and the RFS were 98.3 and 93.3%, respectively.

Discussion

In the present study, a retrospective analysis of the prognosis of stage IB-IIA node-negative CC was performed using the GOG score after RH and trachelectomy. Furthermore, to the best of our knowledge, the present study was the first to involve the evaluation of prognosis based on the scoring system in Japan. The GOG score system that was used was first published by Delgado *et al* (4). They provided a retrospective evaluation of the prognosis of stage IB CC of the phenotype SCC without any adjuvant therapy. Kridelka *et al* (5) determined the criteria for the management of lymph node-negative stage IB uterine CC after RH and demonstrated the evaluation of therapeutic outcome based on these criteria. In contrast to the previous report by Delgado *et al* (4), the criteria of Kridelka *et al* (5)also included other pathological types, such as adenocarcinoma. The criteria indicated that the higher-risk group with a GOG score >120 must receive small-field pelvic radiation and the lower-risk group with a GOG score ≤120 must be monitored closely without adjuvant therapy. At our institute, the GOG score has been used for the indication of adjuvant therapy after RH since 2007. The validity of the criteria for the intermediate risk of CC has been controversial and each institute has used various criteria independently. Yahata *et al* (9) reported that their institute defined intermediate risk as the patient having at least one of the following: Deep stromal invasion >1/3, lymph vascular space invasion and bulky tumor >4 cm. Kim *et al* (10) defined deep stromal invasion as invasion depth/cervical wall >1/2. They indicated that the patients with intermediate risk factors of CC require adjuvant therapy. On the contrary, Cibula *et al* (11) reported the outcome for patients with no adjuvant radiotherapy for intermediate risk with lymph node-negative CC. The recurrence rate was 6.3% (eight out of 127) and the 5-year disease-specific survival rate was 95.7%. They performed type C2 RH for all patients without adjuvant radiotherapy and obtained better outcomes than the present study.

The most well-known criteria were reported by Sedlis *et al* (12) in the GOG study #92 trial and they determined the systematic eligibility criterion, which requires at least 2 of the following risk factors: >1/3 stromal invasion, LVSI and large clinical tumor diameter of 4 cm or more. Adjuvant radiotherapy for the eligible patients reduced the risk of recurrence and prolonged progression-free survival in the follow-up study (13). The outcome of this follow-up study is referred to as the Sedlis criteria, according to which adjuvant radiotherapy is adopted for negative nodes, negative margins and negative parametrium of CC in the NCCN Guidelines version 4.2019 CC (4). On the other hand, additional opinions to judge the intermediate risk of patients with CC after surgery were published. Using more simplified criteria, Cao *et al* (14) reported that the patients who were defined as having intermediate-risk CC based on the criteria did not necessarily require adjuvant therapy to prevent recurrence. They emphasized that LVSI was the only independent prognostic factor. On the contrary, when the criteria were examined in more detail, Chu *et al* (15) reported on the validation of risk stratification using a machine learning algorithm in addition to the Sedlis criteria. This risk stratification consisted of age, LVSI, stromal invasion, size and type of adjuvant therapy, and was able to indicate expected OS and disease-free survival (DFS) 2 and 5 years after surgery (15). These expected OS and DFS rates were derived based on the time-dependent receiver operating characteristic (ROC) curves and the area under the ROC curve. In the present study, it was hypothesized that the risk stratification is able to easily predict the expected OS and DFS; however, this was difficult to use as an indication for detecting low risk or intermediate risk of CC after surgery.

Table I. Patients' characteristics (n=61).

Item	Total	Recurrence	P-value	Died of disease	P-value
Age, years			0.00816		0.0639
20-29	4	0		0	
30-39	15	0		0	
40-49	17	0		0	
50-59	10	0		0	
60-69	9	3		2	
70-	6	1		0	
Stage (FIGO2008)			1		1
IB1	50	4		2	
IB2	5	0		0	
IIA	6	0		0	
Procedure			1		1
Radical hysterectomy + PLN	59	4		2	
Radical trachelectomy + PLN	2	0		0	
Histology			0.534		0.0705
SCC	36	2		0	
Adenocarcinoma	19	1		1	
Adenosquamous carcinoma	6	1		1	
Tumor size, cm			0.89		0.83
<1	8	0		0	
≥1, <2	8	0		0	
≥2, <3	13	1		0	
≥3, <4	24	3		2	
≥4, <5	7	0		0	
≥5	1	0		0	
DOI			0.254		0.76
Superficial	20	0		0	
Middle	22	3		1	
Deep	19	1		1	
LVSI			0.113		0.492
Positive	31	4		2	
Negative	30	0		0	
GOG score			1		0.384
≤120	48	3		1	
Patients who received chemotherapy	1[a]	0		0	
>120	13	1		1	
Patients who received radiation therapy	0	0		0	
Patients who received chemotherapy	1	1		1	
Patients who refused adjuvant therapy	2	0		0	

[a]A case of double cancer received adjuvant chemotherapy for endometrial cancer. PLN, pelvic lymphadenectomy; SCC, squamous cell carcinoma; DOI, depth of invasion; LVSI, lymph vascular space invasion; FIGO, International Federation of Gynecology and Obstetrics.

Regarding the outcomes of the present study, prognoses differed according to the different categories of the GOG score. The outcome of group B (GOG score >40 and ≤70) was not different from that of group A (GOG score ≤40). Based on the above findings, a GOG score ≤70 may require no other adjuvant therapy. When comparing the Sedlis criteria to the GOG scoring system, certain criteria, namely positivity for LVSI, superficial stromal invasion and clinical tumor diameter of ≥5, were associated with a considerably low GOG score. Evaluation of a GOG score ≤70 may imply that the use of the Sedlis criteria leads to overtreatment. By contrast, 5-year RFS of group C (GOG score >70 and ≤120) was worse than that of group D (GOG score >120). Although 1 patient in group D died of disease after adjuvant

Table II. Characteristics of the patients with recurrence.

Age, years	Stage	Histology	DOI, mm (invasion/ cervical wall)	LVSI	Site of recurrence	GOG score	Adjuvant therapy	Disease-free interval, months	Survival period, months	Outcome
61	IB1	Adenosquamous	10 / 20	+	Pelvic floor, PAN	89.76	None	46	60	DOD
73	IB1	SCC	6 / 8	+	Pelvic floor	89.76	None	20	78	Alive
68	IB1	SCC	10 / 15	+	Liver	90.44	None	34	91	Alive
62	IB1	Adenocarcinoma	16 / 22	+	Pelvic floor	183.6	TC 3 cycles	27	66	DOD

DOI, depth of invasion; LVSI, lymph vascular space invasion; PAN, paraaortic lymph node; DOD, died of disease; SCC, squamous cell carcinoma; TC, paclitaxel and carboplatin.

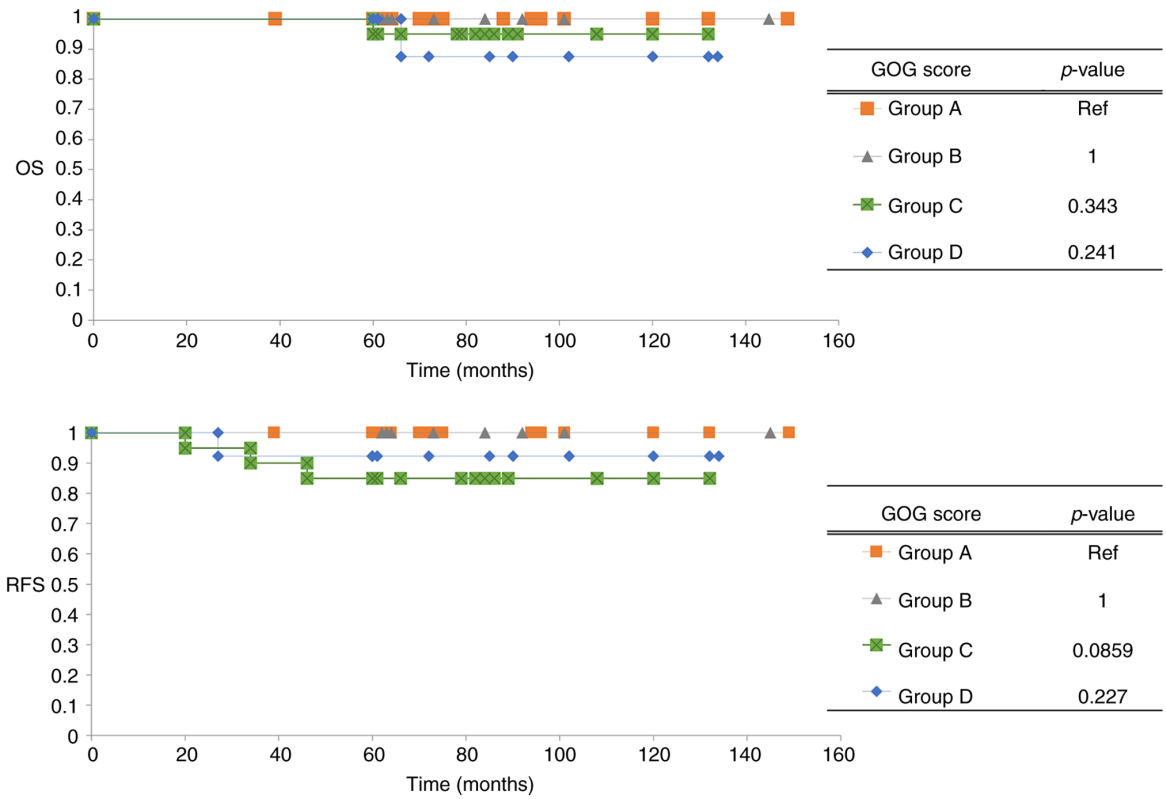

Figure 2. Kaplan-Meier curves of OS and RFS according to the groups stratified by the GOG score and log-rank test for P-value comparisons of group A and the others. Groups based on GOG score: A, ≤40; B, >40 and ≤70; C, >70 and ≤120; and D, >120. OS, overall survival rate; RFS, recurrence-free survival rate; GOG, Gynecology Oncology Group.

chemotherapy, other patients who received adjuvant radiotherapy were still alive without any evidence of disease. In group D, 5-year OS and 5-year RFS were 100 and 92.3%, respectively. Kridelka *et al* (5) reported that the recurrence rate after small-field pelvic radiation for patients with a GOG score of 120 or higher was 4% (one out of 25). Yeo *et al* (16) evaluated the outcome of patients with a GOG score >40 and ≤120, and those with GOG >120 received small-field radiotherapy and standard-field radiotherapy (whole pelvic radiation). The recurrence rates in the groups with a GOG score >40 and ≤120, and >120 were 2.78% (one out of 36) and 4% (one out of 25), respectively. No patient died of CC. Compared to these studies, the outcome of the present study in group D followed a similar trend. On the other hand, the outcome of the patients in group C (GOG score, >70 and ≤120) was not significantly different from that of group A. However, in group C, three patients had recurrence and one patient died of disease. Two patients with SCCs survived after additional therapy and one patient with adenosquamous carcinoma died of disease progression after recurrence. Regarding recurrent cases from group C, the GOG score ranged from 89.76 to 90.44. It was not possible to clarify any appropriate standard, which may exist for the range of group C (GOG score, >70 and ≤120). Ideally, each factor should be analyzed after accumulation and review of patients from group C.

Table III. Five-year OS and RFS rates according to the groups stratified by GOG score.

A, OS

Group based on GOG score	n	5-year OS	SD	95% CI
A	19	1	NA	NA
B	8	1	NA	NA
C	20	0.95	0.049	0.695-0.993
D	13	1	NA	NA

B, RFS

Group based on GOG score	n	5 year-RFS	SD	95% CI
A	19	1	NA	NA
B	8	1	NA	NA
C	20	0.85	0.080	0.604-0.949
D	13	0.92	0.074	0.566-0.989

Groups based on GOG score: A, ≤40; B, >40 and ≤70; C, >70 and ≤120; and D, >120. GOG, Gynecology Oncology Group; OS, overall survival rate; RFS, recurrence-free survival rate; SD, standard deviation; CI, confidence interval.

Of note, four cases of recurrence had several features in common, such as an age of sixty years or more, positivity for LVSI, >1/2 stromal invasion and clinical tumor diameter of 2 cm or more. The pathological types were SCC (2 cases), adenocarcinoma (1 case) and adenosquamous carcinoma (1 case). The first three cases in Table II belonged to group C (GOG score >70 and ≤120) and their GOG score ranged from 89.76 to 90.44. In group C, eleven cases other than three recurrent cases had higher GOG scores than those of these three. It was hypothesized that the probability of recurrence may not depend on a high GOG score. Based on other criteria, these cases were indicated to require adjuvant therapy. Nakamura *et al* (17) defined three factors (positivity for LVSI, >1/2 stromal invasion and clinical tumor diameter of ≥2 and <4) as intermediate risk factors and these cases satisfied all factors. Similarly, these cases also satisfied indications for adjuvant therapy according to the Sedlis criteria (18). It should be noted that cases with a GOG score ≤120 may include cases with indications for adjuvant therapy based on other criteria.

There were certain limitations to the present study. First, the sample size of the present study was too small to evaluate the prognosis using the GOG score for stage IB-IIA node-negative CC precisely, as this was a single institutional study. At the beginning of the present study, it was intended to evaluate the validity of a GOG score ≥120 as an indication of adjuvant therapy. Eventually, only the prognosis of the four groups stratified by the GOG score was compared. Furthermore, a single institutional study has a problem of guaranteeing surgical outcomes if the institute has a low surgical volume. Matsuo *et al* (19) reported that the prognosis for early-stage CC after RH was associated with the institutional surgical volume. In addition, the original study reported by Delgado *et al* (4) indicated that a GOG score >120 correlated with a 40% risk of recurrence. The study was designed to evaluate the prognosis of only the SCC type of CC. However, in the present study, the indications, including the other pathological types, were determined by reference to the criteria reported by Kridelka *et al* (5), which suggested that patients with a GOG score ≥120 receive small-field external beam radiotherapy. Several multivariate analyses indicated that adenocarcinoma had a poorer prognosis than SCC (20-22). It is worth acknowledging that prognosis should ideally be analyzed using samples divided into each pathological type.

In conclusion, a GOG score ≤70 was suggestive of no recurrence without adjuvant therapy. However, the risk of a GOG score >70 differed by reference to risk factors that constitute the GOG score. The current cutoff for adjuvant therapy (GOG score >120) should be further discussed.

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Availability of data and materials

All the datasets generated or analyzed during the present study are included in this published article.

Authors' contributions

YK, YM and KY conceptualized this study. YK performed the data analysis. TO, from the perspective of a radiologist, advised the gynecologists on adjuvant therapy. YA, MM, KH, HH, TU, TK and SK acquired the clinical data. YK and YM drafted the manuscript. YK and YM checked and approved the authenticity of raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The current retrospective study was approved by the Ethics Committee of Medical Research, University of Occupational and Environmental Health (Fukuoka, Japan; approval reference no. H30-160). Information about the study and how patients are able to opt out was posted on the website of the hospital.

Patient consent for publication

Not applicable.

Competing interests

All authors declare that they have no competing interests.

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