



# Prognostic factors for post-recurrence survival among patients with locally advanced cervical cancer who underwent definitive concurrent chemoradiation

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## ABSTRACT

**Background:** The prognostic factors affecting post-recurrence survival (PRS) in patients with locally advanced cervical cancer (LACC) who receive concurrent chemoradiation (CCRT) are not well established. This study aimed to assess the prognostic factors for PRS in patients with recurrent LACC who underwent CCRT as the primary treatment.

**Materials and methods:** We retrospectively reviewed the medical records of patients with a first recurrence of cervical cancer (stage IB2–IVA), who were initially treated with CCRT and completed the planned radiotherapy from 2002 to 2018. Multivariate analysis of independent factors for PRS was performed with the Cox proportional-hazards model.

**Results:** Of 1,658 patients with LACC primarily treated with CCRT, 424 (25.6%) had recurrence, with 142, 125, and 157 patients having locoregional, distant, and combined recurrence, respectively. Approximately 75% of recurrence cases were detected within 2 years after completed treatment, and 81.8% of cases demonstrated symptoms at recurrence diagnosis. The median PRS was 8.4 months, and the 1- and 5-year PRS rates were 36.0% and 5.3%, respectively. Multivariate analysis found that the recurrence-free interval (RFI) ( $p < 0.001$ ), recurrence pattern ( $p < 0.001$ ), white blood cell count ( $p < 0.001$ ), and treatment at recurrence ( $p < 0.001$ ) were independent prognostic factors for PRS.

**Conclusion:** The prognosis of recurrent LACC initially treated with CCRT was notably poor. RFI, recurrence pattern, white blood cell count, and treatment at recurrence were independent prognostic factors for PRS.

**Key words:** cervical cancer; recurrence; prognosis; concurrent chemoradiation

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## Introduction

Currently, patients with locally advanced cervical cancer (LACC) have satisfactory treatment outcomes with concurrent chemoradiation (CCRT), which is a standard treatment for this patient group. A meta-analysis found a 6% improvement in 5-year overall survival with CCRT compared with radiation alone [1]. However, 21.1–30.1% of

patients with LACC treated with CCRT experience recurrence [2–4], with 71.5–91.7% of recurrence cases being detected within 2 years [2, 3, 5]. Recurrence could be locoregional, distant, or combined; distant recurrence was found to be predominant after CCRT in a study by Kobayashi et al. [2], whereas Kozaki et al. [4] reported that locoregional recurrence was the primary pattern after CCRT. Treatment modalities after recurrence are limited

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and depend on the previous initial treatment, pattern of recurrence, extension of recurrence, and patient performance status (PS) [5–7]. Previous studies found that patients with recurrence had a poor prognosis, with a median post-recurrence survival (PRS) of 16.4–18 months [2, 4].

Identifying the clinicopathologic factors that affect survival after recurrence is important because these factors can be used to predict patient prognosis after recurrence and to counsel the patients. Currently, there is limited information on prognostic factors for PRS in patients with LACC that primarily received CCRT. Moreover, only a few studies, which included a small number of recurrence cases initially treated with CCRT or radiotherapy alone, have reported about these prognostic factors [3–5]. Furthermore, some important prognostic factors that could be associated with PRS were not included in the aforementioned studies [3–5].

Therefore, we conducted this study to evaluate the prognostic factors for PRS in patients with recurrent LACC initially treated with CCRT at a tertiary hospital in Southern Thailand.

## Materials and methods

This study was conducted with the approval of the Human Ethics Committee of our institution (IRB number REC.62-303-7-4). We initially included 1,810 patients with cervical cancer stage IB2–IVA (according to International Federation of Gynecology and Obstetrics 2009), who were treated with primary CCRT and completed the planned radiotherapy between December 2002 and December 2018. Patients with incomplete response after primary CCRT ( $n = 118$ ), histologic subtype other than squamous cell carcinoma, adenocarcinoma (AC), and adenosquamous carcinoma (ASC) ( $n = 34$ ), were excluded. Of the remaining 1,658 patients, 424 (25.6%) developed recurrence, and we retrospectively reviewed their medical records and data in the Songklanagarind cancer registry.

The patient, disease, and treatment characteristics at initial diagnosis and first recurrence were collected for all eligible patients. The initial diagnosis data consisted of histology and staging. The data at first recurrence included recurrence pattern (loco-regional, distant, combined), age at recurrence diagnosis, Eastern Cooperative Oncology Group (ECOG) PS, recurrence-free interval (RFI), symp-

toms at recurrence, method of recurrence detection, hemoglobin level, white blood cell (WBC) count, platelet count, and treatment modalities after recurrence.

All eligible patients were primarily treated with definitive CCRT. Radiotherapy consisted of external beam radiotherapy (EBRT) and high-dose-rate intracavitary brachytherapy (HDR-ICBT). EBRT was delivered to the whole pelvis or whole pelvis and paraaortic area, in case of paraaortic lymph node involvement. The typical arrangement for the whole-pelvis radiotherapy included opposed anterior-posterior fields or four-field box depending on the physician's decision. The total EBRT dose to whole pelvis was 45–50 Gy in 1.8–2 Gy daily fractions, delivered 5 days per week. Thereafter, a parametrium boost to 54–60 Gy was applied in some patients with parametrium and/or pelvic wall involvement, or at physician's discretion. HDR-ICBT was delivered at 6.5–7 Gy to point A in 4 fractions, once a week. The total dose to point A in most patients was 80–85 Gy in small-volume tumors ( $\leq 4$  cm) and 85–90 Gy in large-volume tumors. Weekly chemotherapy (cisplatin alone) was delivered concurrently with radiotherapy in all eligible patients.

Follow-up was performed 1 month after completion of the primary CCRT and then every 3 months in the first year, every 4 months in the second year, every 6 months in the third to fifth year, and annually thereafter. History taking and physical, pelvic, and rectal examinations were performed in all eligible patients at every follow-up visit. Cervicovaginal cytology, complete blood count, biochemistry profile, and chest radiography were performed annually. Annual computed tomography (CT) of the pelvis, abdomen, and/or chest, or magnetic resonance imaging (MRI) of the pelvis was not routinely performed unless clinically indicated. Positron emission tomography-CT scan is unavailable in our institution and was not used in all eligible patients. A diagnosis of recurrence was based on patient history, physical and pelvic examination, imaging of suspicious lesion, and/or pathological confirmation. Treatment of recurrent disease depended on previous initial treatment, site and extension of recurrence, and patient PS. In this study, treatment at recurrence comprised surgery, chemotherapy, radiotherapy, CCRT, and palliative care, with chemotherapy being the main

treatment. Palliative care was defined as treatment for symptom relief and/or best supportive care. RFI was defined as the time from the completion of primary CCRT to recurrence. PRS was calculated as the time from recurrence diagnosis to death or the last known follow-up.

Comparisons of clinicopathological characteristics between patterns of recurrence were performed using the Chi-square test and Fisher's exact test for categorical variables. Descriptive statistics were used for patient characteristics and are presented as frequencies and percentages. Survival rates were calculated using the Kaplan-Meier method, and the survival curves of each clinicopathological factors were compared using the log-rank test. Multivariate analysis of independent factors for PRS was performed using the Cox proportional-hazards model. Statistical significance was set as  $p < 0.05$ . All analyses were performed using R version 3.6.1.

## Results

### Patients and pattern of recurrence

Of the 1,658 patients with LACC, who were initially treated with primary CCRT, completed the planned radiotherapy, and did not meet the exclusion criteria, 424 (25.6%) developed recurrence and were included in this study. The clinicopathologic characteristics at initial diagnosis according to recurrence pattern are shown in Table 1; 142 (33.5%), 125 (29.5%), and 157 (37.0%) patients had locoregional, distant, and combined recurrence, respectively. The histologic subtypes were significantly different between the three recurrence patterns ( $p < 0.001$ ). Locoregional recurrence was sig-

nificantly the most common recurrence pattern in patients with AC histology. However, the stage at initial diagnosis did not significantly differ between the three recurrence patterns.

The median age at recurrence diagnosis was 51.7 years. More than 80% of the patients had symptoms at the time of recurrence. Asymptomatic recurrence was mainly detected via physical/pelvic examination (34/77 patients, 44.2%). The median RFI was 12.9 [interquartile range (IQR), 7.9–25.4] months; 73.8%, 85.4%, and 96.9% of the patients were diagnosed with recurrence within 2, 3, and 5 years, respectively. The recurrence rate of anemia, leukocytosis, and thrombocytosis were 42.7%, 27.5%, and 34.5%, respectively. The major treatment modality at recurrence was chemotherapy (53.9%), followed by palliative care (33.1%) (Tab. 2).

### Survival analysis

The median follow-up time after the first recurrence was 6.8 [interquartile range (IQR): 2.8–13.6] months. The median PRS was 8.4 (IQR, 7.3–9.2) months. The 1- and 5-year PRS rates were 36.0% [95% confidence interval (CI): 31.4–41.2] and 5.3% (95% CI: 3.0–9.2), respectively. Univariate analysis found that ECOG performance status (PS) at recurrence ( $p \leq 0.001$ ), RFI ( $p \leq 0.001$ ), pattern of recurrence ( $p \leq 0.001$ ), symptom status ( $p \leq 0.001$ ), hemoglobin level ( $p \leq 0.001$ ), WBC count ( $p \leq 0.001$ ), platelet count ( $p \leq 0.001$ ), and treatment at recurrence ( $p \leq 0.001$ ) were significant prognostic factors for PRS (Tab. 3). Other factors, including histology, stage, and age, were also included in the univariate analysis but were not significant (Tab. 3).

In the multivariate analysis, RFI [hazard ratio (HR) = 0.7; 95% CI: 0.5–0.8 for RFI > 1

**Table 1.** Clinicopathologic characteristics at initial diagnosis after definitive concurrent chemoradiation with respect to recurrence pattern in patients with recurrent cervical cancer (n = 424)

Variable/At initial diagnosis	All patients (n = 424)	Locoregional recurrence (n = 142)	Distant recurrence (n = 125)	Combined recurrence (n = 157)	p-value
<b>Histology</b>					
Squamous cell carcinoma	298 (70.3)	81 (57.1) <sup>a</sup>	100 (80.0) <sup>b</sup>	117 (74.5) <sup>b</sup>	< 0.001
Adenocarcinoma	106 (25.0)	52 (36.6) <sup>a</sup>	20 (16.0) <sup>b</sup>	34 (21.7) <sup>b</sup>	
Adenosquamous carcinoma	20 (4.7)	9 (6.3)	5 (4.0)	6 (3.8)	
<b>Stage at initial diagnosis</b>					
IB2–IIB	222 (52.4)	83 (58.5)	64 (51.2)	75 (47.8)	0.173
IIIA–IVA	202 (47.6)	59 (41.5)	61 (48.8)	82 (52.2)	

Values are presented as n (%); <sup>a,b</sup>recurrence patterns not having a superscript in common within clinicopathological characteristics differ significantly ( $p < 0.05$ )

**Table 2.** Clinicopathologic characteristics at recurrence diagnosis in patients with recurrent cervical cancer after definitive concurrent chemoradiation (n = 424)

Variable	Total (n = 424) n (%)
<b>Age [years]</b>	
< 40	49 (11.6)
40–55	218 (51.4)
> 55	157 (37.0)
<b>ECOG score</b>	
0–1	221 (52.2)
2–4	202 (47.8)
<b>Pattern of recurrence</b>	
Locoregional	142 (33.5)
Distant	125 (29.5)
Combined	157 (37.0)
<b>Symptoms</b>	
No	77 (18.2)
Yes	345 (81.8)
<b>Method of recurrence detection</b>	
Symptom	345 (81.7)
Physical/pelvic examination	34 (8.1)
Cervicovaginal cytology	8 (1.9)
Chest radiography	16 (3.8)
CT/MRI	19 (4.5)
<b>Recurrence-free interval (years)</b>	
≤ 2	313 (73.8)
> 2	111 (26.2)
<b>Hemoglobin level [g/dL]</b>	
≤ 10	181 (42.7)
> 10	222 (52.4)
<b>White blood cell count [/<math>\mu</math>L]</b>	
≤ 10,000	292 (72.5)
> 10,000	111 (27.5)
<b>Platelet count [/<math>\mu</math>L]</b>	
≤ 400,000	264 (65.5)
> 400,000	139 (34.5)
<b>Treatment at recurrence</b>	
Surgery	4 (1.0)
Chemotherapy	220 (53.9)
Radiation	47 (11.5)
Concurrent chemoradiation	2 (0.5)
Palliative care	135 (33.1)

ECOG — Eastern Cooperative Oncology Group; CT — computed tomography, MRI — magnetic resonance imaging

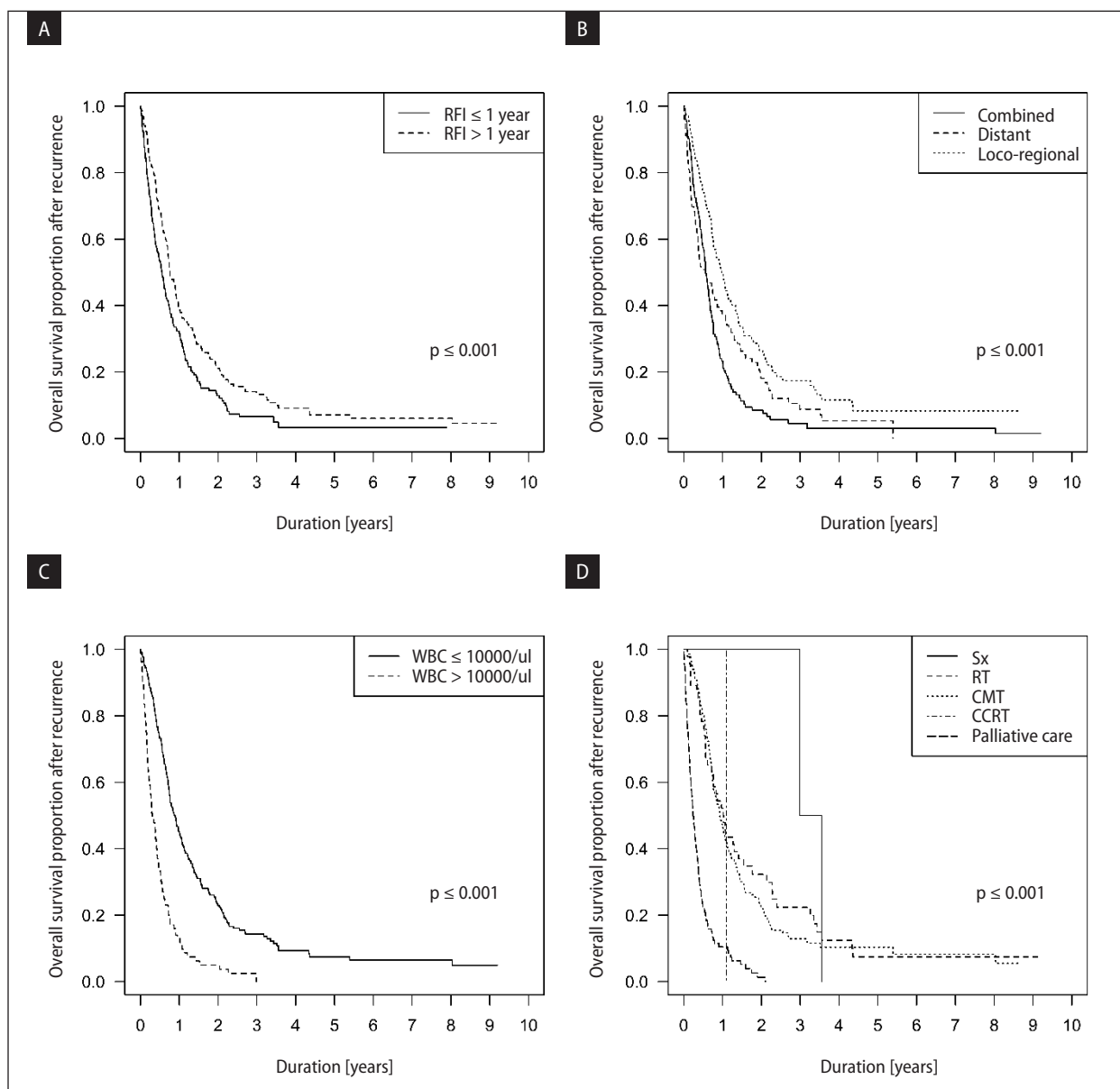
year;  $p < 0.001$ ) (Fig. 1A), pattern of recurrence (HR = 1.5; 95% CI: 1.1–2.0 for distant, HR = 1.7, 95% CI: 1.3–2.2 for combined;  $p < 0.001$ ) (Fig. 1B), WBC count (HR = 2.0; 95% CI: 1.5–2.7 for WBC count > 10,000/ $\mu$ L;  $p < 0.001$ ) (Fig. 1C), and treat-

**Table 3.** Univariate analysis of prognostic factors affecting 1-year overall post-recurrence survival

Variables	1-year overall survival (%) (95% CI)	p-value
<b>At initial diagnosis</b>		
<b>Histology</b>		
Squamous cell carcinoma	33.9 (28.6–40.1)	0.400
Adenocarcinoma	38.0 (29.2–49.5)	
Adenosquamous carcinoma	54.2 (36.0–81.6)	
<b>Stage</b>		
IB2–IIB	37.6 (31.3–45.3)	0.400
IIIA–IVA	34.1 (27.9–41.6)	
<b>At first recurrence diagnosis</b>		
<b>Age [years]</b>		
< 40	39.3 (27.1–57.1)	0.700
40–55	33.1 (27.0–40.6)	
> 55	38.6 (31.4–47.4)	
<b>ECOG score</b>		
≤ 1	54.6 (48.0–62.0)	< 0.001
> 1	15.1 (10.6–21.6)	
<b>Recurrence-free interval [years]</b>		
≤ 1	31.8 (25.6–39.3)	< 0.001
> 1	39.6 (33.3–47.1)	
<b>Symptoms</b>		
No	66.1 (55.8–78.2)	< 0.001
Yes	28.6 (23.9–34.2)	
<b>Pattern of recurrence</b>		
Locoregional	49.5 (41.5–59.0)	< 0.001
Distant	37.3 (29.2–47.8)	
Combined	23.3 (17.3–31.4)	
<b>Hemoglobin level [g/dL]</b>		
≤ 10	26.0 (19.9–33.8)	< 0.001
> 10	44.3 (37.8–51.8)	
<b>White blood cell count [/<math>\mu</math>L]</b>		
≤ 10,000	45.0 (39.3–51.5)	< 0.001
> 10,000	13.0 (7.9–21.5)	
<b>Platelet count [/<math>\mu</math>L]</b>		
≤ 400,000	44.6 (38.7–51.4)	< 0.001
> 400,000	19.3 (13.3–28.1)	
<b>Treatment at recurrence</b>		
Surgery	100	< 0.001
Chemotherapy	46.9 (40.3–54.5)	
Radiation	52.2 (39.6–68.8)	
Concurrent chemoradiation	100	
Palliative care	10.5 (6.2–17.8)	

CI — confidence interval; ECOG — Eastern Cooperative Oncology Group

ment at recurrence (HR = 8.7, 95% CI: 2.7–28.6 for palliative care;  $p < 0.001$ ) (Fig. 1D) were independent prognostic factors for a poor PRS (Tab. 4).



**Figure 1.** Survival after recurrence according to recurrence-free interval (RFI) (A), pattern of recurrence (B), white blood cell count (WBC) (C), and treatment at recurrence (D). Sx — surgery; RT — radiotherapy; CMT — chemotherapy; CCRT — concurrent chemoradiation

## Discussion

The percentage of LACC recurrence (25.6%) in our study was observed to be consistent with that in previous studies (21.1–30.1%); these studies mainly included cases of LACC initially treated with CCRT [2–4]. Combined recurrence was the most common pattern of recurrence in the current study (37%). These results suggest that recurrence of primary LACC was mostly discovered at an advanced stage of disease. Our results are not consistent with those from earlier studies with heterogeneity of

stage, initial workup modalities, initial treatment with CCRT or radiotherapy alone which found that distant recurrence was the most common recurrence pattern [2, 8]. In addition, one study that included a small number of patients with persistent disease found that local recurrence was the major recurrence pattern [4]. The present study found that locoregional recurrence was significantly more frequent than other recurrence patterns in patients with AC histology. Our result is in accordance with that of Yokoi et al. [9]; in their study, 94.4% of LACC patients received CCRT, and the AC/ASC

**Table 4.** Multivariate analysis of prognostic factors for overall post-recurrence survival

Variable	HR	95% CI	p-value
<b>Recurrence-free interval [years]</b>			< 0.001
≤ 1	1	–	
> 1	0.7	0.5–0.8	
<b>Pattern of recurrence</b>			< 0.001
Locoregional	1	–	
Distant	1.5	1.1–2.0	0.004
Combined	1.7	1.3–2.2	< 0.001
<b>Hemoglobin level [g/dL]</b>			0.184
≤ 10	1	–	
> 10	0.8	0.7–1.1	
<b>White blood cell count [/<math>\mu</math>L]</b>			< 0.001
≤ 10,000	1	–	
> 10,000	2.0	1.5–2.7	
<b>Platelet count [/<math>\mu</math>L]</b>			0.970
≤ 400,000	1	–	
> 400,000	1.0	0.8–1.3	
<b>Treatment at recurrence</b>			< 0.001
Surgery	1	–	
Chemotherapy	2.7	0.8–8.7	0.099
Radiation	3.0	0.9–10.1	0.072
Concurrent chemoradiation	3.2	0.3–32.7	0.318
Palliative care	8.7	2.7–28.6	< 0.001

HR — hazard ratio; CI — confidence interval

group (1/16 patients had ASC) had a higher proportion of locoregional recurrence (20%) than distant (11.9%) and combined recurrence (0%), but a p-value was not calculated. These results may be explained by the radioresistant nature of AC histology [10–14]; thus, patients with AC have a high possibility of microscopic disease in the pelvis even after treatment [15]. Our study proposes that patients with AC should receive more intensive local treatment.

Regarding symptoms at recurrence, the majority of those with recurrence (81.4%) in the current study had symptoms at the diagnosis of recurrence, which is in line with a previous study of early-stage cervical cancer from the same institute, which found more cases of symptomatic (63.1%) than asymptomatic (33.3%) recurrence [16]. In the current study, physical/pelvic examination was able to detect a high percentage of cases of asymptomatic recurrence (44.2%). Similarly, a systematic review by Elit et al. [17] found that complete physical examination detected the largest number of recurrence cases (29–71%). Hence, physical/pelvic examination is one of the important methods

for recurrence detection and should be thoroughly performed at every follow-up visit.

Radiologic imaging in our study, including chest radiography and CT/MRI, had a moderate rate of recurrence detection (20.8% and 24.7%, respectively), which is also concordant with the aforementioned systematic review [17]. However, a Japanese study [5] reported a high rate of detection of asymptomatic recurrence (65%) via radiologic imaging, which is higher than noted in our report and in the systematic review by Elit et al. [17]. This may be because the surveillance protocol in the Japanese study included an intensive follow-up program that involved frequent radiologic imaging. One probable reason our study found a high proportion of symptomatic recurrence was because follow-up imaging studies were not routinely performed based on our follow-up protocol, which caused some asymptomatic cases of recurrence to be missed. Thus, routine radiologic imaging during the follow-up period seems essential and requires further investigation.

Considering cervicovaginal cytology, our result showed the lowest rate of recurrence detection in



asymptomatic patients with this method (10.4%), which is in accordance with a previous systematic review that showed that 0–17% of patients with recurrence were detected with cervicovaginal cytology [17]. However, currently, the role of HPV-DNA testing as a follow-up tool is arousing interest. A recent systematic review and meta-analysis in India that included 10 cohort studies reported high sensitivity (0.84, 95% CI: 0.66–0.94) but low specificity (0.35, 95% CI: 0.20–0.54) of HPV-DNA testing for recurrence detection after pelvic irradiation [18]. Thus, the current practice guidelines do not recommend HPV-DNA testing for surveillance [19–21].

In the present study, the patients had a relatively short RFI, with approximately 75% of the patients experiencing recurrence within 2 years. Our study is in accordance with previous research on locally advanced stage [2, 3, 5]. Nonetheless, we found that the proportion of patients with RFI within 2 years in our study was larger than noted in a study of early-stage disease at the same institute, which reported that less than half of patients were detected with recurrence within 2 years [16]. Since locally advanced stage tumors have more aggressive clinical behavior than early-stage tumors.

The median PRS (8.4 months) of patients in our study was notably poor and was shorter than that noted in two preceding-CCRT era studies (16.4–18 months) [2,4]. These differences may be because 15% of the patients in the study by Kabayashi et al. [2] were stage IB1, while there was no patient with stage IB1 in our study. Moreover, the Kozaki et al. study [4] included only patients that received chemotherapy as the treatment at recurrence which indicated that their study had a higher percentages of patients with good PS than our study. Our study also had a high percentage of patients with ECOG PS 2–4 at recurrence (47.8%), who probably could not receive intensive treatment, resulting in the poor PRS. Concerning the prognostic factors for PRS, previous studies that mainly included LACC patients who were initially treated with CCRT or radiotherapy alone found that RFI [4], site of recurrence [3,5] and treatment modalities at recurrence [5] were independent prognostic factors for PRS as noted in our study. Moreover, it is interesting that the current study found that leukocytosis (WBC count > 10,000/ $\mu$ L) was a novel independent prognostic factor, which has been uniden-

tified by previous studies on LACC initially treated with CCRT; however, our result corresponds with an early-stage study at the same institute, which also found that leukocytosis was an independent prognostic factor for PRS [16]. The mechanism of leukocytosis with respect to recurrence and its adverse effect on PRS were evaluated in some studies [22, 23]. These studies revealed that many hematopoietic growth factors, particularly granulocyte-colony stimulating factor, are involved in the leukocytosis mechanism and promote rapid tumor progression, which is related to the poor survival in this group of patients [22, 23]. Thus, we suggest that leukocytosis at recurrence should be considered a prognostic factor for PRS in patients with LACC who are initially treated with CCRT.

The strength of this study is that it includes a large number of patients with recurrent LACC only primarily treated with CCRT. There were also some limitations to this study. First, this study was retrospective, and selection and confounding biases are unavoidable in this study type. Second, the long-term treatment period might have introduced a time-trend bias which is an inevitable limitation. Finally, the treatment modalities at recurrence were influenced by the previous initial treatment, patient's PS, patient's personal characteristics, including education and socioeconomic status, and physician preferences.

In conclusion, the prognosis of patients with recurrent LACC initially treated with CCRT was notably poor. RFI, pattern of recurrence, WBC count, and treatment at recurrence were independent prognostic factors for PRS. Physical examination/pelvic examination was one of the important recurrence detection methods during the follow-up period. Furthermore, the role of routine surveillance imaging is worthy of additional study.

#### Conflicts of interest

None declared.

#### Funding

None declared.

#### Authors' contributions

P.T. conceptualized the study. P.T., N.J., and A.T. were equally involved in the data collection. P.T. was responsible for the data analysis, data interpretation, and manuscript writing.

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