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Clinical implication of surgically treated early-stage cervical cancer with multiple high-risk factors

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Objective: Presence of high-risk factor in cervical cancer is known to be associated with decreased survival outcomes. However, the significance of multiple high-risk factors in early-stage cervical cancer related to survival outcomes, recurrence patterns, and treatment implications is not well elucidated.

Methods: A retrospective study was conducted for surgically treated cervical cancer patients (stage IA2–IIB, n=540). Surgical-pathological risk factors were examined and tumors expressing ≥1 high-risk factors (nodal metastasis, parametrial involvement, or positive surgical margin) were eligible for analysis (n=177, 32.8%). Survival analysis was performed based on the number of high-risk factors and the type of adjuvant therapy.

Results: There were 68 cases (38.4%) expressed multiple high-risk factors (2 high-risk factors: n=58, 32.8%; 3 high-risk factors: n=10, 5.6%). Multiple high-risk factors remained an independent prognosticator for decreased survival outcomes after controlling for age, histology, stage, and treatment type (disease-free survival: hazard ratio [HR], 2.34; p=0.002; overall survival: HR, 2.32; p=0.007). Postoperatively, 101 cases (57.1%) received concurrent chemoradiotherapy (CCRT) and 76 cases (42.9%) received radiotherapy (RT) alone. CCRT was beneficial in single high-risk factor cases: HRs for CCRT over RT alone for cumulative risk of locoregional and distant recurrence, 0.27 (p=0.022) and 0.27 (p=0.005), respectively. However, tumor expressing multiple high-risk factors completely offset the benefit of CCRT over RT alone for the risk of distant recurrence: HR for locoregional and distant recurrence, 0.31 (p=0.071) and 0.99 (p=0.980), respectively.

Conclusion: Special consideration for the significance of multiple high-risk factors merits further investigation in the management of surgically treated early-stage cervical cancer.

Keywords: Combined Modality Therapy; Neoplasm Recurrence, Local; Retrospective Studies; Risk Factors; Survival Analysis; Uterine Cervical Neoplasms

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INTRODUCTION

Despite global efforts to eliminate cervical cancer in the past decades by early detection or prevention, cervical cancer remains the most deadly gynecologic malignancy in the world [1]. In 2008, over a half million women were diagnosed with cervical cancer, and approximately a quarter million women died from this disease [1]. Cervical cancer is clinically staged, and hysterectomy-based surgery is a choice of treatment with

a curative intent in early-stage disease. Depending on the pattern of surgico-pathological risk factors obtained from the surgical specimen, postoperative adjuvant radiotherapy (RT) is indicated for patients with an increased risk of recurrence [2]. Surgico-pathological risk factors for cervical cancer are categorized into high-, intermediate-, or low-risk based on the type of histologic findings [3-5]. High-risk factors include pelvic lymph node metastasis, parametrial involvement, and positive surgical margins [4]. Intermediate-risk factors include large tumor size, lymphovascular space invasion, and deep cervical stromal invasion [3,5]. These classifications were originally designed to identify the subgroup of patients who were at risk of recurrence. Such patients are believed to benefit from additional RT after radical hysterectomy and have improved survival outcomes [6].

When the tumor is confined within the cervix, the prognosis is generally favorable exceeding a 5-year survival rate of 80% [3,7,8]. However, the presence of high-risk factor in the tumor is associated with poorer survival outcomes of early-stage cervical cancer. The 5-year survival rate drops to 50% to 70% when a tumor expresses a high-risk factor [4]. One of the limitations of this traditional risk factor classification is that the impact of multiple high-risk factors on survival outcomes is not completely understood [9,10]. While at least two risk factors are required for a cervical cancer patient to be considered part of the intermediate-risk factor group, only one risk factor is necessary to be classified as part of the high-risk factor group. However, tumors may potentially exhibit more than two high-risk factors. Indeed, over 10% of surgically treated early-stage cervical cancers are reported to exhibit multiple high-risk factors (12.6%) [11]. In addition, the significance of multiple high-risk factors in early-stage cervical cancer in terms of recurrence pattern and postoperative adjuvant therapy has not been examined although distinctive pattern of distant recurrence was increased in the patients with high-risk factors [12,13].

The aim of this study was to evaluate the significance of multiple high-risk factors in the survival of surgically treated early-stage cervical cancer patients. The implication of multiple high-risk factors was further investigated to assess the treatment response of postoperative adjuvant therapy based on recurrence patterns.

MATERIALS AND METHODS

1. Clinical information

Upon approval of the study protocol by the Institutional Review Boards at Osaka University Hospital and Osaka Medical Center for Cancer and Cardiovascular Diseases, a previous study database for cervical cancer cases was utilized [11]. Inclusion criteria were cases who underwent radical hysterectomy for stage IA2–IIB cervical cancer that expressed at least one high-risk factor in the surgical specimen between January 1998 and December 2008. Cases with para-aortic lymph node (PALN) involvement and histology types other than squamous cell carcinoma, adenocarcinoma, and adenosquamous carcinoma were not included in the study. Per our routine practice, surgical specimens were examined by two independent gynecologic pathologists and the aforementioned Surgico-pathological risk factors and histology types were recorded based on the World Health Organization system for tumors of the uterine cervix [14]. The cervical cancer was clinically staged according to the International Federation of Gynecology and Obstetrics (FIGO) staging criteria at the time of initial diagnosis. PALNs were preoperatively evaluated with a computed tomography (CT) scan of the abdomen as part of the routine initial evaluation. Subsets of the cases evaluated in the current study were within the context of the previous studies [11,15-18].

2. Treatment

Type III radical hysterectomy with pelvic lymphadenectomy was performed in all the cases by eight surgeons, as described previously [16]. Lymphadenectomy included complete bilateral pelvic lymphadenectomy aiming for the removal of all external iliac, internal iliac, common iliac, obturator, suprainguinal, and presacral lymph nodes systematically. PALNs were assessed by manual palpation during the surgery, and nodal resection for histologic evaluation was performed for the cases with intraoperatively palpable or suspicious nodes on preoperative CT scan.

Postoperative adjuvant RT is indicated when the tumor expresses any of the high-risk prognostic factors or one of the intermediate-risk prognostic factors. Whole pelvis RT with concurrent administration of platinum chemotherapy (concurrent chemoradiotherapy, CCRT) has been our standard practice since January 1999 as reported previously [15-17], and patients before 1999 and who declined CCRT received pelvic RT alone without chemotherapy. At our institutions, nedaplatin is used as the radio-sensitizing agent for cervical cancer. Nedaplatin was given intravenously during the course of RT, as reported previously [15,17,19]. No patient received neoadjuvant chemotherapy prior to surgery.

Postoperative pelvic RT was performed using 10-MV X-rays delivered from a linear accelerator using the anteroposterior parallel opposing technique. The superior and inferior margin of the external radiation field was the upper border of the fifth lumber vertebra and the inferior border of the obturator foramen, respectively. Laterally, the field extended 2 cm beyond

the lateral margin of the bony pelvic wall. We used multileaf collimators to block the upper and lower corners of the radiation field. External irradiation was delivered to the whole pelvis at 2 Gy per fraction in five fractions per week for a total of 25 fractions (50 Gy).

Patients whose pathological reports revealed multiple pelvic node metastases were treated with extended field radiotherapy (EFRT) without concurrent chemotherapy. The radiation field encompassed the pelvic and PALN drainage area. The superior margin of the PALN area was the bottom of the T12 vertebral body, and the inferior margin was the inferior border of the obturator foramen. The lateral margin was 1.5 to 2 cm lateral to the widest point of the bony pelvis. External irradiation was delivered to the EFRT fields for a total of 45 Gy in 25 fractions and to the whole pelvis at 1.8 Gy per fraction for a total of 28 fractions (50.4 Gy).

Table 1. Patient characteristics (n=177)

Characteristic	No. (%)
Age (yr), mean±SD	50±10.9
Clinical stage*	
IA2	0
IB1	52 (29.4)
IB2	20 (11.3)
IIA	28 (15.8)
IIB	77 (43.5)
Histology	
Squamous	136 (76.8)
Adenocarcinoma	36 (20.3)
Adenosquamous	5 (2.8)
High-risk factor	
LN metastasis	133 (75.1)
PM invasion	103 (58.2)
RM involvement	19 (10.7)
Postoperative adjuvant therapy	
None	0
Concurrent chemoradiotherapy	101 (57.1)
Radiotherapy alone	76 (42.9)
Recurrence	67 (37.9)
Locoregional alone	22 (32.8)
Distant alone	43 (64.2)
Locoregional+distant	2 (3.0)

LN, lymph node; PM, parametrium; RM, resection margin.
*Clinical stage at the time of initial diagnosis.

3. Definition

Disease-free survival (DFS) was defined as the time interval between the initial surgery and the first recurrence. If there was no recurrence, DFS was defined as the time interval between the initial surgery and the last follow-up. Overall survival (OS) was defined as the time interval between the initial surgery and the date of death or last follow-up. Locoregional recurrence was defined as cancer recurrence in the pelvis within the radiation field. Among the 35 cases who received EFRT indicated for multiple pelvic nodal metastasis, there were six cases that developed recurrence in the PALNs within the radiation field, and these recurrences were counted as locoregional recurrence. Distant recurrence was defined as cancer recurrence in the organ-site outside the radiation field.

4. Statistical analysis

The primary interest of study was to determine survival out-comes based on the extent of high-risk factors. The secondary interest was to examine recurrence patterns and to evaluate treatment implications of adjuvant therapy based on the extent of high-risk factors. Continuous variables were assessed for normality (Kolmogorov-Smirnov test) and expressed as appropriate (mean±SD or median with range). Significance of time-dependent outcomes including DFS and OS was examined with log-rank test. Cox's proportional hazard regression test was used for multivariate analysis. Survival curves were constructed with Kaplan-Meier method. p-values of less than 0.05 were considered statistical significant (2-tailed). The SPSS ver. 21.0 (IBM Co., Armonk, NY, USA) was used for all analyses.

Table 2. Patterns of high-risk factor in early-stage cervical cancer (n=177)

Variable	No. (%)
Single high-risk factor	
LN metastasis alone	68 (38.4)
PM invasion alone	38 (21.5)
RM involvement alone	3 (1.7)
Multiple high-risk factors	68 (38.4)
Double high-risk factors	
LN+PM	52 (29.4)
LN+RM	3 (1.7)
PM+RM	3 (1.7)
Triple high-risk factors	
LN+PM+RM	10 (5.6)

LN, lymph node; PM, parametrium; RM, resection margin.

RESULTS

Among the 540 patients who underwent radical hysterectomy for early-stage cervical cancer, there were 177 cases (32.8%) that had at least one high-risk factor in the tumor and were included in the analysis. The clinical demographics are shown in **Table 1**. Mean age at diagnosis was 50, and the most common clinical stage was IIB (43.5%) followed by IB1 (29.4%). The majority of histology was squamous cell carcinoma (76.8%). Among the type of high-risk factors, pelvic lymph node metastasis was the most commonly seen in the study (75.1%) followed by parametrial invasion (58.2%). Postoperatively, all

the study cases received adjuvant therapy: 101 cases (57.1%) for CCRT and 76 cases (42.9%) for RT alone. Median follow-up time was 56.8 months (range, 6.4 to 171 months). There were 67 cases who developed recurrence. Distant recurrence alone (64.2%) was the most common pattern of recurrence followed by locoregional recurrence alone (32.8%). Among the 45 cases of distant recurrence, multiple recurrent organ-sites were seen in nearly half of the cases (n=21, 46.7%). The most common organ-site for distant recurrence was PALNs (outside the radiation field, n=17, 37.8%) followed by lung (n=12, 26.7%) and supraclavicular lymph nodes (n=10, 22.2%). The most common organ-site for locoregional recurrence was vagina
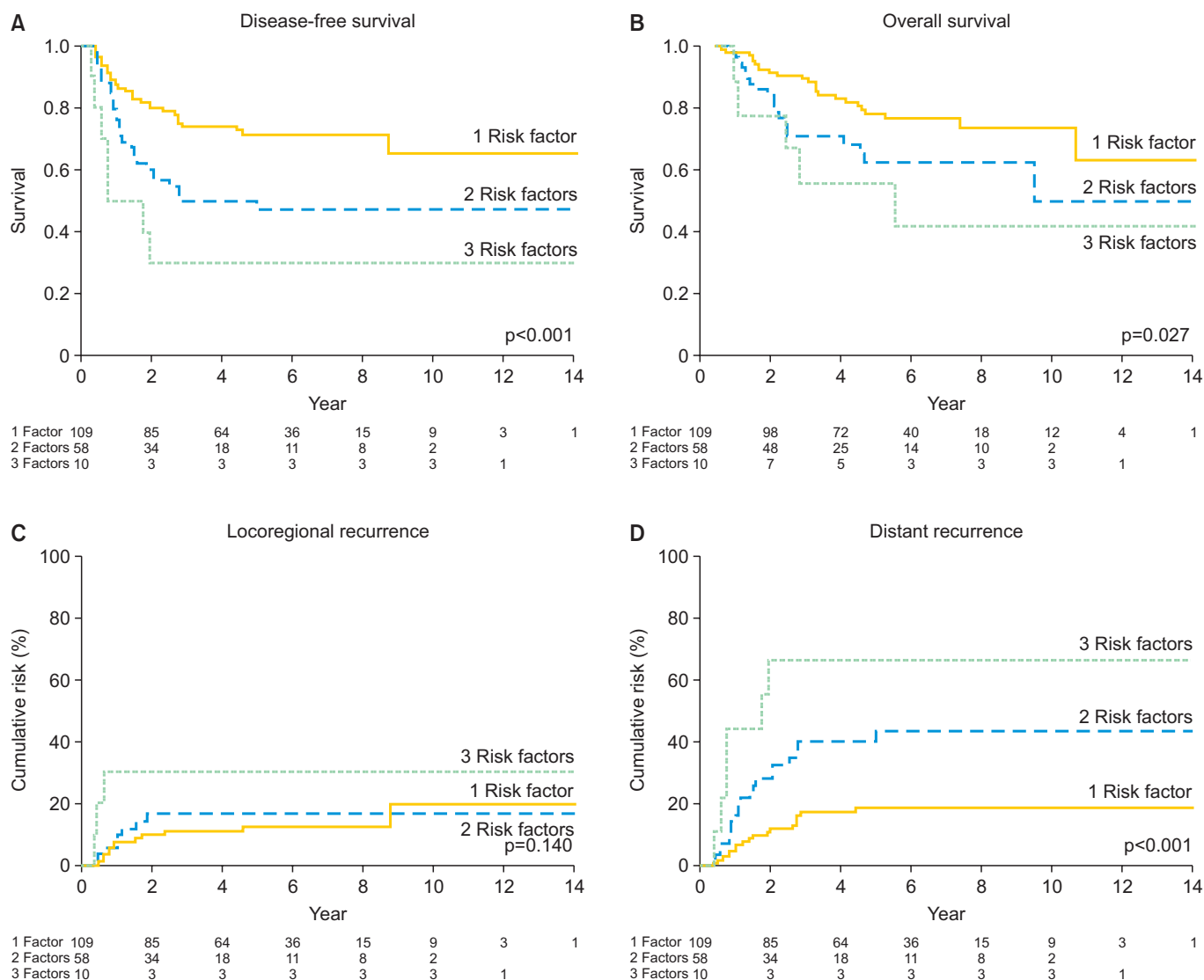

Fig. 1. Multiple high-risk factors and survival outcomes of early-stage cervical cancer. Numbers at risk are shown per group at the bottom of each figure. (A) Disease-free survival and (B) overall survival based on the number of high-risk factors (lymph node metastasis, parametrium invasion, and resection margin involvement). Cumulative risks for (C) locoregional and (D) distant recurrence are shown based on the number of high-risk factors.

(n=13, 54.2%) followed by pelvic side wall (n=10, 41.7%).

Among the 177 cases, 68 cases (38.4%) had multiple high-risk factors. Of those, 58 cases (32.8%) had two high-risk factors, and 10 cases (5.6%) had three high-risk factors. Patterns of high-risk factor expressions in early-stage cervical cancer are shown in **Table 2**. Among cases with single high-risk factor (n=109, 61.6%), pelvic lymph node metastasis alone was the most common pattern (38.4%) followed by parametrial invasion alone (21.5%). Among cases with multiple high-risk factors (n=68, 38.4%), a combination of pelvic lymph node metastasis and parametrial invasion was the most common pattern (29.4%).

Survival analysis was performed. Five-year DFS rates for cases with 1, 2, and 3 high-risk factors were 71.2%, 50.3%, and 30%, respectively (p<0.001) (**Fig. 1A**). Five-year OS rates for cases with 1, 2, and 3 high-risk factors were 78.2%, 62.3%, and 55.9%, respectively (p=0.027) (**Fig. 1B**). In univariate analysis, DFS was associated with histologic type (5-year rate, adenocarcinoma/adenosquamous vs. squamous, 34.3% vs. 70.7%; hazard ratio [HR], 3.04; 95% confidence interval [CI], 1.86 to 4.97; p<0.001), clinical stage (II vs. I, 55.1% vs. 72.2%; HR, 2.12; 95% CI, 1.25 to 3.62; p=0.004), number of high-risk factors (multiple vs. single, 47.4% vs. 71.2%; HR, 2.32; 95% CI, 1.44 to 3.77; p<0.001), and adjuvant therapy (CCRT vs. RT alone, 72.7% vs. 47.8%; HR, 0.43; 95% CI, 0.26 to 0.69; p<0.001). In multivariate analysis after controlling for age (p=0.30), histology (p<0.001), clinical stage

(p=0.32), and adjuvant therapy (p=0.013), multiple high-risk factors remained an independent prognosticator associated with poor DFS of early-stage cervical cancer (HR, 2.34; 95% CI, 1.39 to 3.96; p=0.002) (**Table 3**). For OS, histology (adenocarcinoma/adenosquamous vs. squamous; HR, 2.95; 95% CI, 1.67 to 0.20; p<0.001), number of high-risk factors (multiple vs. single; HR, 2.07; 95% CI, 1.18 to 3.63; p=0.009), and adjuvant therapy (CCRT vs. RT alone, 77.9% vs. 63.7%; HR, 0.48; 95% CI, 0.27 to 0.85; p=0.01) were significantly associated with decreased OS; however, clinical stage did not reach statistical significance (p=0.068). After controlling for age (p=0.91), histology (p<0.001), clinical stage (p=0.82), and adjuvant therapy (p=0.055), multiple high-risk factors remained an independent prognosticator for poor OS (HR, 2.32; 95% CI, 1.26 to 4.29; p=0.007) (**Table 3**).

Patterns of recurrence were examined based on the number of high-risk factors. Locoregional recurrence within the radiation field was similar across the cases with 1, 2, and 3 high-risk factors (5-year cumulative risk rate, 12.4%, 16.2%, and 33.3%; p=0.14) (**Fig. 1C**). On the contrary, distant recurrence outside the radiation field was significantly increased as tumors expressed more high-risk factors (5-year cumulative risk rate, 18.7%, 39.9%, and 65.3%; p<0.001) (**Fig. 1D**).

The implication of multiple high-risk factors for postoperative adjuvant therapy was examined (**Table 4**). If a high-risk factor was not stratified by the magnitude of factors, CCRT

Table 3. Survival outcomes and multiple high-risk factors in early-stage cervical cancer

Variable	No.	Disease-free survival			Overall survival		
		5 yr (%)	HR (95% CI)	p-value*	5 yr (%)	HR (95% CI)	p-value*
Age (yr)				0.30			0.91
≤50	77	58.1	Reference		71.8	Reference	
>50	100	65.2	0.77 (0.47–1.26)		72.2	1.04 (0.58–1.87)	
Histology				<0.001			<0.001
SCC	136	70.7	Reference		80.3	Reference	
Adeno/AS	41	34.3	3.17 (1.91–5.27)		46.4	3.20 (1.77–5.77)	
Clinical stage[†]				0.32			0.82
I	72	72.2	Reference		76.6	Reference	
II	105	55.1	1.36 (0.74–2.48)		68.7	1.08 (0.55–2.13)	
High-risk factor				0.002			0.007
Single	109	71.2	Reference		78.2	Reference	
Multiple	68	47.4	2.34 (1.39–3.96)		61.6	2.32 (1.26–4.29)	
Adjuvant therapy				0.013			0.055
RT alone	76	47.8	Reference		63.7	Reference	
CCRT	101	72.7	0.53 (0.32–0.88)		77.9	0.56 (0.31–1.01)	

AS, adenosquamous; CCRT, concurrent chemoradiotherapy; CI, confidence interval; HR, hazard ratio; RT, radiotherapy; SCC, squamous cell carcinoma; 5 yr (%), 5-year survival rate.
*Multivariate Cox proportional hazard regression test. [†]Clinical stage at the time of initial diagnosis.

was shown to be more effective than RT alone for controlling locoregional (5-year cumulative recurrence rate , 7.3% vs. 25.2%; HR 0.25; 95% CI, 0.10 to 0.64; p=0.002) and distant (5-year cumulative recurrence rate, 22.0% vs. 36.9%; HR, 0.54; 95% CI, 0.30 to 0.96; p=0.033) recurrence in cases with any number of high-risk factors. However, when a high-risk factor was stratified by the number of risk factors (multiple vs. single), the benefit of CCRT over RT alone in controlling recurrence disappeared. Five-year cumulative recurrence rate of CCRT was significantly lower than that of RT alone for controlling both locoregional recurrence (6.5% vs. 22.2%; HR, 0.27; 95% CI, 0.08 to 0.89' p=0.022) (**Fig. 2A**) and distant recurrence (9.6% vs. 34.3%; HR, 0.27; 95% CI, 0.10 to 0.71; p=0.005) (**Fig. 2B**) in cervical cancer with a single high-risk factor. Five-year cumulative recurrence rates of CCRT and RT alone in cases with multiple high-risk factors, however, were similar in controlling locoregional recurrence (9.7% vs. 28.9%; HR, 0.31; 95% CI, 0.08 to 1.19; p=0.071) (**Fig. 2C**) and distant recurrence (45.7% vs. 40.0%; HR, 0.99; 95% CI, 0.46 to 2.12; p=0.98) (**Fig. 2D**). Similar results were seen for survival analysis, and CCRT was beneficial only for tumors expressing a single high-risk factor: HR for DFS, 0.27; 95% CI, 0.13 to 0.57; p=0.001; and HR for OS, 0.31; 95% CI, 0.13 to 0.72; p=0.007, respectively. The survival benefit of CCRT diminished when tumors expressed multiple high-risk factors: HR for DFS, 0.72; 95% CI, 0.37 to 1.38; p=0.32; and HR for OS, 0.78; 95% CI, 0.36 to 1.73; p=0.55, respectively. Similarly, when cases with squamous cell carcinoma histology were analyzed (n=136), the distant recurrence rates were not statistically different between RT alone and CCRT groups in early-stage cervical cancer with multiple-high risk factors (5-year cumulative rate, 27.5% vs. 37.3%; HR, 1.08; 95% CI, 0.41 to 2.83; p=0.88).

DISCUSSION

Tumors presenting multiple high-risk factors in early-stage cervical cancer are not rare, and accounted for more than one third of the high-risk group in our study. Early-stage cervical cancer patients with multiple high-risk factors had similar survival outcomes when compared to advanced-stage disease. When tumors expressed 2 and 3 high-risk factors, 5-year DFS of the patients were 50.3% and 30%, respectively (**Fig. 1A, B**), which are comparable to that of reported 5-year DFS of FIGO stage III cervical cancer, 30% to 50% [2]. To understand the possible causality as to why multiple high-risk factors are associated with decreased survival outcomes, recurrence pattern was examined: the results demonstrated that while there is no difference in the risk of locoregional recurrence after treatment irrespective of the number of high-risk factors, there was a significantly increased risk of distant recurrence in cervical cancer tumors with multiple high-risk factors (5-year cumulative risk of distant recurrence in 2 and 3 high-risk factors, 39.9% and 65.3%, respectively) (**Fig. 1C, D**). These results are comparable to the risk of distant recurrence in advanced-stage disease reported in the previous study (10-year cumulative risk after definitive RT, stage III and stage IVA, 39% and 75%, respectively) [20]. These findings support the importance of recognizing double and/or triple high-risk factors in a certain population of early-stage cervical cancer patients with considerably poor survival outcomes, proposed as the "multiple high-risk" group for cervical cancer in our study.

Treatment implications for cervical cancer with multiple high-risk factors warrant further discussion. Our results showed that multiple high-risk factors offset the benefit of additional platinum-based chemotherapy during RT after surgi-

**Table 4.** Postoperative adjuvant therapy and multiple high-risk factors in early-stage cervical cancer

Variable	No.	Locoregional recurrence			Distant recurrence		
		5 yr (%)	HR (95% CI)	p-value*	5 yr (%)	HR (95% CI)	p-value*
Any high-risk factor (all)				0.002			0.033
RT alone	76	25.2	Reference		36.9	Reference	
CCRT	101	7.3	0.25 (0.10–0.64)		22.0	0.54 (0.30–0.96)	
Single high-risk factor				0.022			0.005
RT alone	43	22.2	Reference		34.3	Reference	
CCRT	66	6.5	0.27 (0.08–0.89)		9.6	0.27 (0.10–0.71)	
Multiple high-risk factors				0.071			0.98
RT alone	33	28.9	Reference		40.0	Reference	
CCRT	35	9.7	0.31 (0.08–1.19)		45.7	0.99 (0.46–2.12)	

CCRT, concurrent chemoradiotherapy; CI, confidence interval; HR, hazard ratio; RT, radiotherapy; 5 yr (%), 5-year cumulative risk.
*Log-rank test.

Single high-risk factor
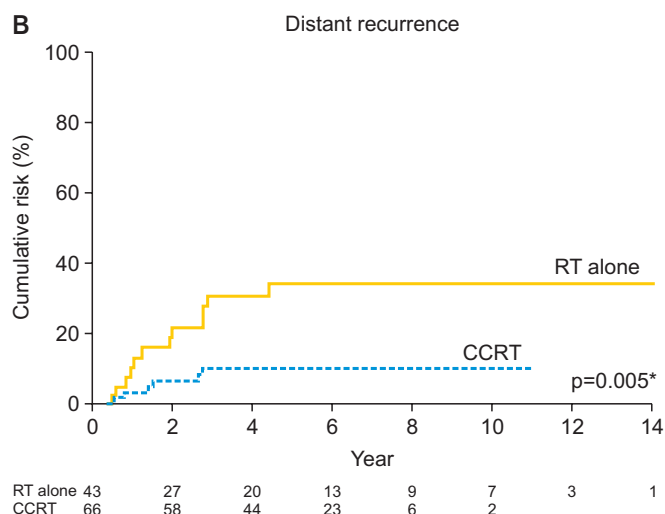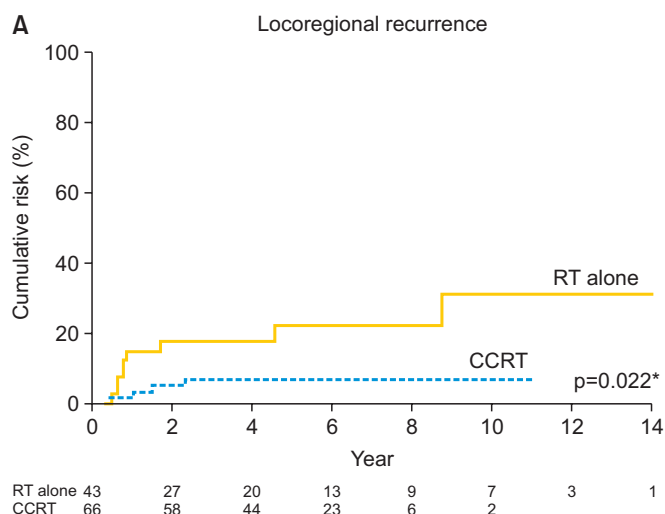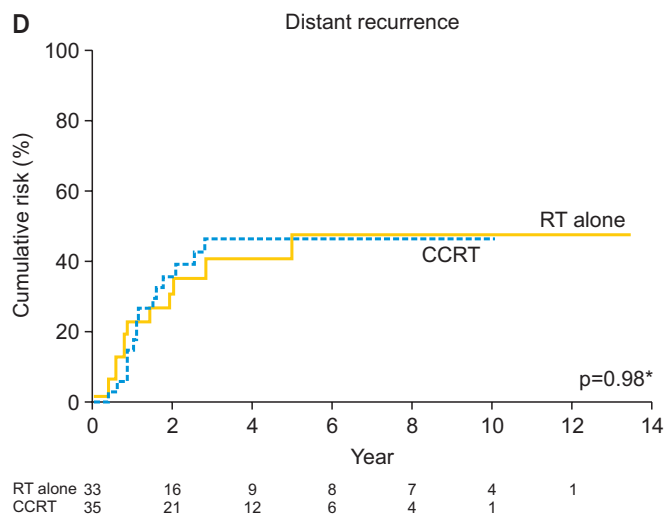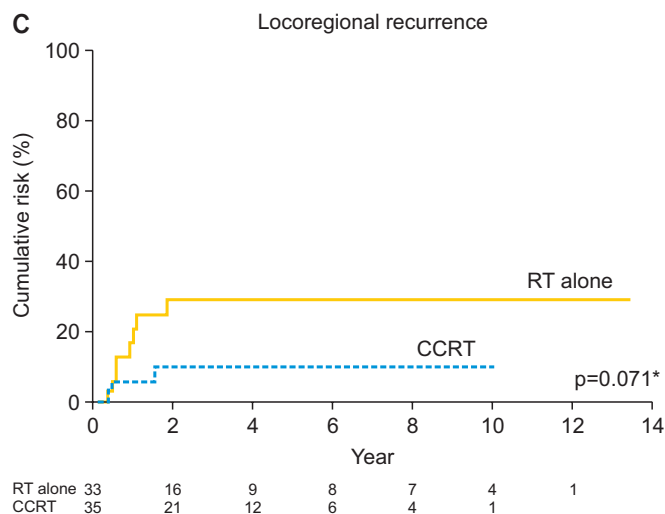
Fig. 2. Multiple high-risk factors and recurrent pattern in early-stage cervical cancer. Numbers at risk are shown per group at the bottom of each figure. Cumulative risks for (A) locoregional and (B) distant recurrence are shown based on adjuvant therapy type in single high-risk factor cases. Cumulative risks for (C) locoregional and (D) distant recurrence are shown based on adjuvant therapy type in multiple high-risk factor cases. RT, radiotherapy; CCRT, concurrent chemoradiotherapy. *Log-rank test.

cal treatment (**Table 4**, **Fig. 2**). This finding was clearly evident for the risk of distant recurrence in the group with multiple high-risk factors demonstrating complete abolishment of survival advantage in CCRT over RT alone group (HR, 0.99) (**Fig. 2D**). More importantly, without stratifying the extent of high-risk factors, our overall findings support the benefit of an additional radiosensitizing chemotherapy agent during RT both for locoregional and distant recurrence control (HR, 0.25 and 0.54, respectively) (**Table 4**). These results are consistent with the previously reported clinical trial that showed that CCRT decreased the risk of both locoregional and distant recurrence [13]. However, the study did not stratify the number of high-

risk factors as our study did. Further studies will be needed to demonstrate the reproducibility and durability of the impact of multiple high-risk factors in cervical cancer.

It is speculated that these patients with multiple high-risk factors likely have occult distant metastases that could not be sterilized by additional platinum-based chemotherapy and radiosensitization. As the concurrent administration of cisplatin-based chemotherapy during RT is a standard practice for postoperative adjuvant therapy for the high-risk group, additional therapeutic approaches are needed to improve the survival outcomes in the particular population belonging to the "multiple high-risk" group. A considerable proportion

of cervical cancer patients in the high-risk group exhibited multiple high-risk factors (38.4%) and can be considered part of the "multiple high-risk" group. These multiple high-risk factor tumors did not show benefits of CCRT over RT alone and resulted in survival outcomes similar to advanced-stage disease. Because of these outcomes, the indication and efficacy of consolidation with systemic chemotherapy after postoperative adjuvant treatment needs to be considered in the future [21-23]. Vrdoljak et al. [21] examined the efficacy of four cycles of ifosamide and cisplatin administered after the completion of primary treatment with CCRT for 62 stage IB2–IVA cervical cancer patients. The results showed 100% of complete response rate with 88.7% of DFS rate after 49 months of median follow-up time. In other study, four cycles of consolidation therapy with paclitaxel and nedaplatin was conducted in 34 stage IIB–IIIB cervical cancer patients that demonstrated 88% of complete response rate and 82% of 2-year DFS rate [22]. In a comparison study for CCRT with or without consolidation therapy with cisplatin and 5-fluorouracil (three cycles) in 78 stage IIB-IVA cervical cancer patients, patients who did not receive consolidation therapy had more risk of distant metastasis when compared to patients received consolidation therapy (23.1% vs. 7.7%, p=0.06) [23]. Given the survival outcomes of multiple high-risk factors patients that were similar to locally advanced disease, the concept of consolidation therapy may be a feasible option in this particular group of early-stage cervical cancer. Gynecologic Oncology Group/Radiation Therapy Oncology Group 0724 is currently undertaking a phase III trial for early-stage cervical cancer with high-risk factor. In this trial, patients treated with radical hysterectomy followed by pelvic RT are randomly assigned to systemic chemotherapy (carboplatin and paclitaxel, every 3 weeks for four cycles) or no treatment [24]. These studies will identify a subset of patient group with high-risk early-stage cervical cancer who has a benefit of additional systemic chemotherapy.

A major strength of our study is our comprehensive approach to examining survival outcomes, recurrence patterns, and effects of postoperative RT of cervical cancer tumors expressing multiple high-risk factors. A potential weakness of the study is that it is retrospective in nature thus factors such as, treatment algorithms including various surgical techniques, chemotherapy protocols, and radiation approaches may be confounded. Another limitation is that we do not have data for how patients were allocated to treatment types (selection bias) and that we do not have information for preoperative suspicious for parametrial involvement and nodal metastasis prior to radical hysterectomy.

In conclusion, evaluation of surgically treated cervical cancer

by the number of high-risk factors demonstrated the ability to understand the aggressiveness of tumor biology. This approach merits further investigation especially in its implication to postoperative adjuvant therapy.

CONFLICT OF INTEREST

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

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