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ORIGINAL ARTICLE

Salvage radiotherapy with or without concurrent chemotherapy for pelvic recurrence after hysterectomy alone for early-stage uterine cervical cancer

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Abstract
Purpose Treatment outcomes of patients with pelvic recurrence after hysterectomy alone for uterine cervical cancer who received salvage radiotherapy (RT) with or without concurrent chemotherapy were investigated.
Methods Salvage RT for recurrent cervical cancer confined to the pelvic cavity after hysterectomy alone was received by 33 patients. The median interval between initial hysterectomy and recurrence was 26 months. Whole-pelvic irradiation was delivered to median dose of 45 Gy, followed by a boost with a median dose of 16 Gy to the gross tumor volume. Cisplatin-based concurrent chemotherapy was administered to 29 patients.
Results The median follow-up period was 53 months for surviving patients. Most patients (97.0%) completed salvage RT of ≥45 Gy. Complete response (CR) was achieved in 23 patients (69.7%). Pelvic sidewall involvement and evaluation with positron-emission tomography-computed tomography were significantly associated with CR. The 5-year progression-free survival (PFS), local control (LC), distant metastasis-free survival (DMFS), and overall survival (OS) rates were 62.7, 79.5, 72.5, and 60.1%, respectively. Initial International Federation of Gynecology and Obstetrics stage, pelvic sidewall involvement, and CR status were significant factors for PFS and OS rates in multivariate analysis. The incidence of severe acute and late toxicities (≥grade 3) was 12.1 and 3.0%, respectively.
Conclusion Aggressive salvage RT with or without concurrent chemotherapy for recurrent cervical cancer confined to the pelvic cavity was feasible, with promising treatment outcomes and acceptable toxicities. However, even more intensive novel treatment strategies should be investigated for patients with unfavorable prognostic factors.

Keywords Uterine cervical neoplasms · Neoplasm recurrence · Chemoradiotherapy · Salvage therapy · Survival

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Salvage-Radiotherapie mit oder ohne gleichzeitige Chemotherapie bei Beckenrezidiv nach alleiniger Hysterektomie im frühen Stadium des Gebärmutterhalskrebses

Zusammenfassung
Zielsetzung Untersuchung der Behandlungsergebnisse von Patientinnen mit Beckenrezidiv nach alleiniger Hysterektomie bei Zervixkarzinom, die eine Salvage-Radiotherapie (RT) mit oder ohne begleitende Chemotherapie erhalten hatten.

Methoden Insgesamt 33 Patientinnen erhielten eine Salvage-RT für ein auf die Beckenhöhle begrenztes Rezidiv des Zervixkarzinoms nach alleiniger Hysterektomie. Der mediane Zeitraum zwischen der Hysterektomie und dem Rezidiv betrug 26 Monate. Die Bestrahlung betraf das gesamte Becken mit einer medianen Dosis von 45 Gy, danach folgte eine Wiederholung mit einer medianen Dosis von 16 Gy auf die gesamte Tumormasse. Eine begleitende cisplatinbasierte Chemotherapie bekamen 29 Patientinnen.
Ergebnisse Der mediane Nachbeobachtungszeitraum für überlebende Patientinnen betrug 53 Monate. Die meisten Patientinnen (97,0 %) schlossen die Salvage-RT mit ≥45 Gy ab. Ein vollständiges Ansprechen („complete response", CR) erreichten 23 Patientinnen (69,7 %). Beckenwandbeteiligung und Beurteilung mittels Positronenemissionstomographie-Computertomographie standen in deutlichem Zusammenhang mit einem CR. Die Raten für progressionsfreies 5-Jahres-Überleben (PFS), lokale Kontrolle (LC), fernmetastasenfreies Überleben (DMFS) und Gesamtüberleben (OS) lagen bei jeweils 62,7 %, 79,5 %, 72,5 % und 60,1 %. In der multivariaten Analyse waren das Stadium gemäß der International Federation of Gynecologists and Obstetricians, die Beckenwandbeteiligung und der CR-Status wichtige Faktoren für die PFS- oder OS-Raten. Die Inzidenz schwerer akuter und später auftretender Toxizitäten (≥Grad 3) betrug 12,1 % bzw. 3,0 %.
Schlussfolgerung Die aggressive Salvage-RT mit oder ohne begleitende Chemotherapie für ein auf die Beckenhöhle begrenztes rezidivierendes Zervixkarzinom ist praktikabel, mit vielversprechenden Behandlungsergebnissen und akzeptablen Toxizitäten. Für Patientinnen mit ungünstigen prognostischen Faktoren sollten intensiver neuartige Behandlungsstrategien untersucht werden.

Schlüsselwörter Uterine Zervixneoplasien · Neoplasierezidiv · Chemotherapie · Salvage-Therapie · Überleben

In early-stage cervical cancer, radiotherapy (RT) and surgery lead to oncologically comparable results, with a different toxicity spectrum [14]. After hysterectomy for early-stage cervical cancer (International Federation of Gynecology and Obstetrics [FIGO] IA1–IIA2), approximately 10–20% of patients have developed recurrences [6]. However, this finding came from earlier studies conducted prior to the introduction of adjuvant treatments. In a recent study, the recurrence rate of selected early-stage cervical cancer patients after hysterectomy alone decreased to a level of <10% [19]. Among all recurrences, up to 75% of cases were clinically limited to the pelvic cavity [1–3, 13, 15].

Due to its rarity, there have been no prospective randomized trials for the treatment of locoregionally recurrent cervical cancer, and the mainstay of treatment has not been established. Instead, salvage RT with or without concurrent chemotherapy is currently recommended on the basis of a low level of evidence in recurrent cervical cancer patients without a previous history of pelvic irradiation [6, 18].

Several studies with limited numbers of patients have reported clinical outcomes of salvage RT with or without concurrent chemotherapy for recurrent cervical cancer [7, 9–12, 16, 17, 21, 23, 24]. However, the majority of these studies were conducted before the early 2000s and therefore did not reflect recent advances in the diagnosis, treatment techniques, and the assessment of treatment response [7, 9–12, 17, 21, 23, 24]. Furthermore, in several studies, a broader patient population was included, as some patients received postoperative RT after an initial hysterectomy and some had recurrent disease in the para-aortic lymph node area [16, 17, 23, 24]. Therefore, the results of these studies should be interpreted with caution in current clinical practice for the treatment of recurrent cervical cancer confined to the pelvic cavity. The purpose of this study was to investigate the treatment outcomes of salvage RT or concurrent chemoradiotherapy (CCRT) in patients with pelvic recurrence after hysterectomy alone for uterine cervical cancer.

Methods

Patients

The Institutional Review Board of Ajou University School of Medicine approved this study and waived informed consent. From 1995 to 2015, all medical records of patients with pelvic recurrence of cervical cancer who received salvage RT at our institution were reviewed. We excluded patients: 1) with recurrent carcinoma in situ, 2) with para-aortic lymph node recurrence or distant metastasis, 3) with a previous history of neo- or adjuvant treatments, and 4) those treated in the palliative setting. The remaining 33 patients were included in the present study. Of these, 5 patients were referred from an outside hospital at the time of recurrence. Recurrence was diagnosed either by histologic confirmation, or by at least two positive findings among elevation of serum squamous cell carcinoma antigen (SCC-Ag), continuously growing mass lesion seen on serial computed tomography (CT) or magnetic resonance imaging (MRI), and positron emission tomography-computed tomography (PET-CT).

Radiotherapy

All patients received salvage RT with a 10–15 MV photon beam. Three-dimensional conformal RT was planned and the whole pelvis was irradiated conventionally using the box technique, with a median dose of 45 Gy (range, 23.4

Table 1 Patient characteristics

Patient characteristic	No. of patients (%)
Age at recurrence	Median 51 years
<40 years	7 (21.2)
≥40 years	26 (78.8)
Initial stage	
0	1 (3.0)
IA1	4 (12.1)
IB1	17 (51.5)
IB2	6 (18.2)
2A1	4 (12.1)
Unknown	1 (3.0)
Type of initial surgery	
Simple hysterectomy	6 (22.2)
Radical hysterectomy	27 (77.8)
Histology	
Squamous cell carcinoma	28 (84.8)
Others	5 (15.2)
Disease-free interval	Median 26 months
≤24 months	16 (48.5)
>24 months	17 (51.5)
Pelvic wall involvement	
Not involved	19 (57.6)
Involved	14 (42.4)
Histologic confirmation	
No	16 (48.5)
Yes	17 (51.5)
Level of SCC-Ag at recurrence	Median 4.2 ng/ml
≤2.0 ng/ml	13 (39.4)
>2.0 ng/ml	19 (57.6)
Unknown	1 (3.0)
Size of recurrent lesion	Median 4.0 cm
≤4.0 cm	22 (66.7)
>4.0 cm	11 (33.3)
PET-CT	
No	18 (54.5)
Yes	15 (45.5)
Treatment	
RT alone	4 (12.1)
CCRT	29 (87.9)
[a]Chemotherapeutic regimen	
Weekly cisplatin	8 (27.6)
Cisplatin + 5-FU	20 (69.0)
Cisplatin + paclitaxel	1 (3.4)
Total radiation dose	Median 61 Gy
<60 Gy	12 (36.4)
≥60 Gy	21 (63.6)

FIGO International Federation of Gynecology and Obstetrics, *SCC-Ag* squamous cell carcinoma antigen, *PET-CT* positron emission tomography-computed tomography, *RT* radiotherapy, *CCRT* concurrent chemoradiotherapy, *5-FU* 5-fluorouracil
[a]Among patients who received concurrent chemotherapy

Table 2 Predictive factors for complete response after salvage treatments

Variable	CR rate (%)	OR[a]	*p*-value[a]
All patients	69.7		
Age at recurrence		0.225	0.095
<40 years	42.9		
≥40 years	76.9		
Initial stage		6.750	0.025
0–FIGO IB1	81.8		
FIGO IB2–IIA	40.0		
Disease-free interval		0.917	0.909
≤24 months	68.8		
>24 months	70.6		
Level of SCC-Ag		1.944	0.413
≤2.0 ng/ml	76.9		
>2.0 ng/ml	63.2		
Size at recurrence		4.250	0.071
≤4.0 cm	81.0		
>4.0 cm	50.0		
Pelvic wall		5.333	0.043
Not involved	84.2		
Involved	50.0		
Total radiation dose		1.500	0.617
<60 Gy	75.0		
≥60 Gy	66.7		
Evaluation with PET-CT		0.071	0.020
No	50.0		
Yes	93.3		

CR complete response, *OR* odds ratio, *FIGO* International Federation of Gynecology and Obstetrics, *SCC-Ag* squamous cell carcinoma antigen, *PET-CT* positron emission tomography-computed tomography
[a]Obtained by univariate logistic regression

to 48.6 Gy). The gross tumor volume was boosted with a median dose of 16 Gy (range, 0 to 24 Gy).

Because the National Health Insurance Service, which is the only insurance benefit provider in our country, only began to approve claims for intensity-modulated RT for recurrent cervical cancer after 2015, it was not possible to apply this high-precision technique to the patients.

Seven patients with stump recurrence received vaginal cuff brachytherapy after completion of external beam RT. Of these, 6 patients received high-dose-rate brachytherapy with a median total dose of 10 Gy in fraction size 4–5 Gy (range, 5 to 21 Gy). Low-dose-rate interstitial brachytherapy was delivered with a total dose of 20 Gy in 1 patient.

Chemotherapy

Cisplatin-based concurrent chemotherapy was administered to 29 patients. The chemotherapeutic regimen was determined according to disease extent, patients' age, and performance status: 8 patients with small stump recurrence

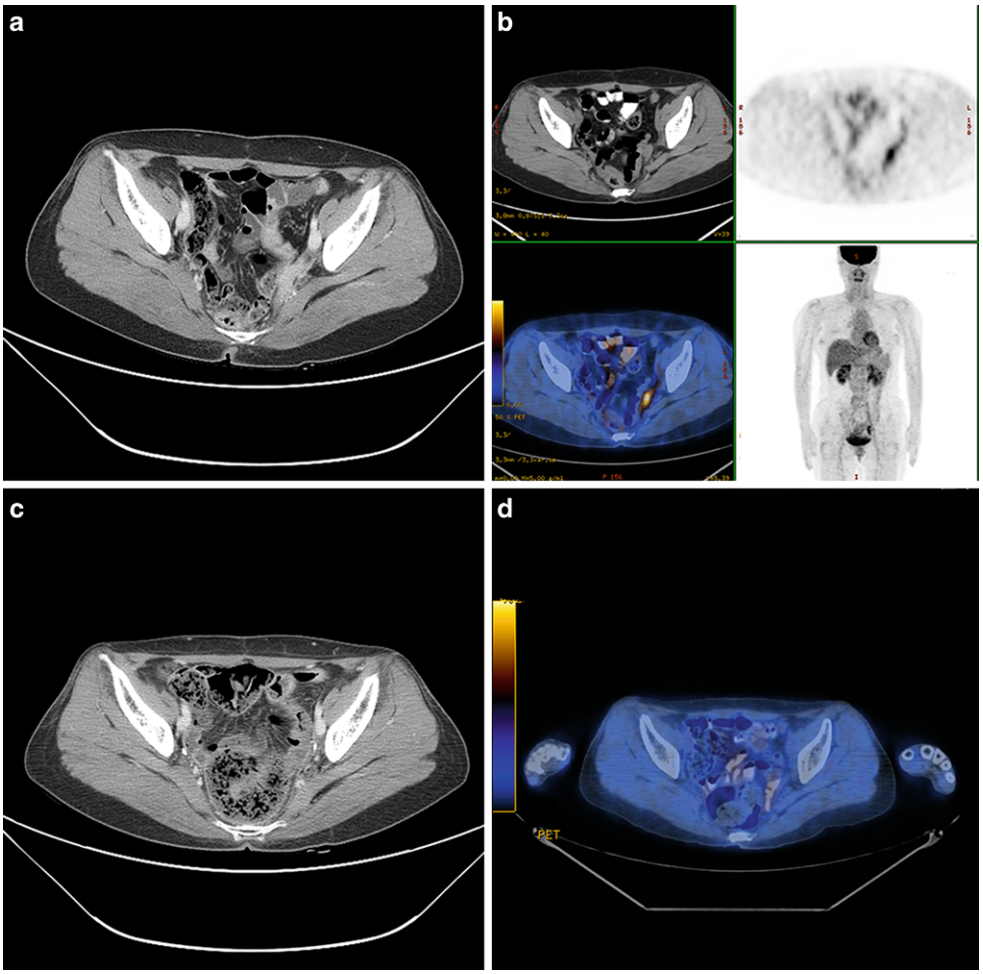

Fig. 1 A 51-year-old woman diagnosed with pelvic recurrence 88 months after radical hysterectomy. **a** Computed tomography (CT) scan showing an ill-defined 4.5 cm-sized soft tissue lesion on the left parametrium with extension to the pelvic sidewall. **b** Positron emission tomography-computed tomography (PET-CT) scan showing a hypermetabolic lesion on the pelvic sidewall corresponding to the mass seen on CT. **c** CT scan 1 year later showing disappearance of the lesion on the pelvic sidewall and **d** PET-CT scan 1 year later showing the disappearance of the lesion on the pelvic sidewall

(≤4.0 cm) received weekly cisplatin (40 mg/m^2 of body surface area administered once a week for up to six cycles); 21 patients received cisplatin (70 mg/m^2 on day 1 of each cycle) combined with 5-fluorouracil (1,000 mg/m^2 on days 2 to 5 of each cycle) repeated every 4 weeks for 4 cycles. Paclitaxel (135 mg/m^2 of body surface area on day 1 of each cycle) combined with cisplatin (60 mg/m^2 of body surface area on day 2 of each cycle) was administered to 1 patient with adenosquamous cell carcinoma for 4 cycles. Maintenance chemotherapy was not administered after completion of RT in any patients.

At the discretion of gynecologic oncologists, 4 patients did not receive concurrent chemotherapy. All of these patients had microscopic or less than 2 cm-sized stump recurrence.

Assessment

After completion of salvage CCRT or RT, all patients were examined regularly by physical examination and/or radiographic imaging work-ups at 3–6 month intervals. Treatment response in patients with clinically visible tumor was determined by radiographic findings and assessed according to the revised Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1) [5]. The treatment response for patients with microscopic disease was evaluated by histological confirmation. Toxicities during or after salvage treatments were evaluated based on the Common Terminology Criteria for Adverse Events, version 4.03.

Statistics

Predictive factors for treatment response were identified using the logistic regression model. All survival rates were calculated from the first day of salvage treatment, using the Kaplan–Meier method. Progression-free survival (PFS) was defined as the time to progression of the target lesion or development of new lesions. Overall survival (OS) was defined as the time to death from any cause or last follow-up. Local control (LC) was defined as the time to disease progression inside the pelvic cavity. Distant metastasis-free survival (DMFS) was defined as the time to development of a new lesion outside the pelvic cavity. Univariate analysis was performed using the log-rank test. Factors with a *p*-

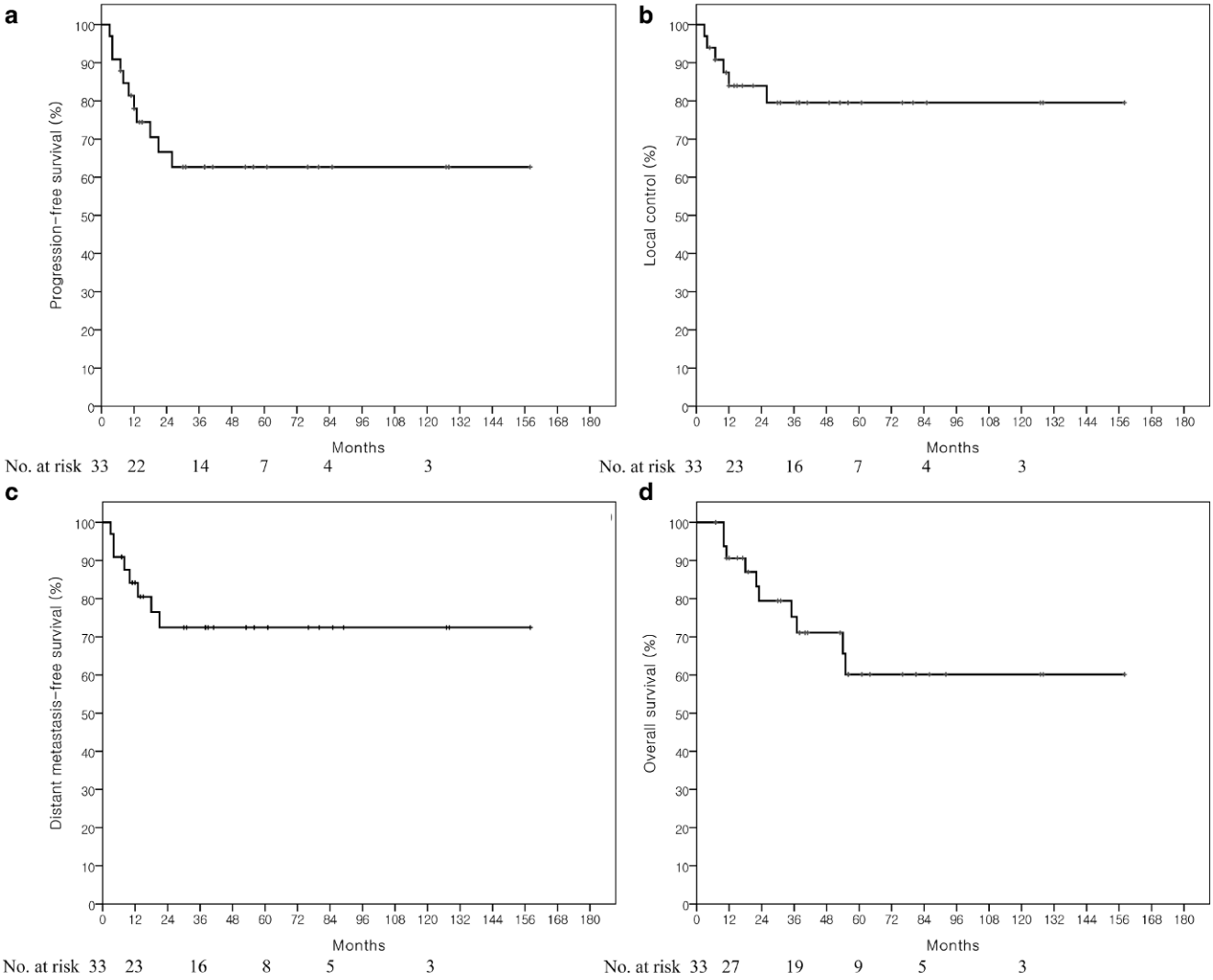

Fig. 2 Kaplan–Meier survival curves of **a** progression-free survival, **b** local control, **c** distant metastasis-free survival, and **d** overall survival

value of <0.10 were entered into multivariate analysis using the Cox proportional hazards model. All statistical analyses were performed using IBM SPSS statistics for Windows version 20.0 (IBM Corp., Armonk, NY, USA).

Results

Patient characteristics

The patient characteristics of the present study are presented in Table 1. The median disease-free interval from the date of hysterectomy to the date of recurrence was 26 months (range, 4 to 88 months). There were 2 patients with adenocarcinoma and 2 patients with adenosquamous cell carcinoma. Patients who received a simple hysterectomy initially had stage 0, FIGO IA1, or unknown stage. In 16 patients, a biopsy was not taken at the time of diagnosis with recurrence. Of these patients, 10 were diagnosed with recurrence by PET-CT (Fig. 1). Other patients were diagnosed by radiographic work-ups and elevated levels of serum SCC-Ag.

Treatment compliance and toxicities

Thirty-two patients completed salvage RT with a minimum dose of 45 Gy, whereas 1 patient refused salvage RT at 23.4 Gy. Among 21 patients who received the combination chemotherapy, 4 did not receive further chemotherapy after completion of salvage RT due to intolerability (n = 3) and refusal of treatment (n = 1).

Severe acute hematologic toxicities (≥grade 3) occurred in 4 patients, all of whom received concurrent cisplatin plus 5-fluorouracil. All of the severe hematologic toxicities were leukopenia and no patients developed febrile neutropenia. All gastrointestinal toxicities during salvage treatments were tolerable. For late toxicities, only 1 patient suffered

Table 3 Univariate analysis for clinical outcomes

	PFS[a]	*p*-value	LC[a]	*p*-value	DMFS[a]	*p*-value	OS[a]	*p*-value
All patients	62.7		79.5		72.5		60.1	
Age at recurrence		0.059		0.012		0.093		0.043
<40 years	35.7		45.7		42.9		35.7	
≥40 years	69.7		86.6		78.9		66.0	
Initial stage		0.001		0.017		<0.001		<0.001
0–FIGO IB1	78.4		88.4		89.5		78.7	
FIGO IB2–IIA	23.3		58.3		26.7		17.5	
Disease-free interval		0.764		0.906		0.939		0.438
≤24 months	67.5		80.4				55.1	
>24 months	57.2		78.2				65.7	
Size at recurrence		0.011		0.038		0.005		0.003
≤4.0 cm	78.9		88.4		90.2		78.7	
>4.0 cm	32.8		63.5		36.5		28.6	
Pelvic wall		0.001		0.016		0.002		0.003
not involved	88.5		94.1		94.4		84.0	
involved	27.2		57.7		39.9		29.1	
Level of SCC Ag		0.271		0.742		0.276		0.357
≤2.0 ng/ml	74.6		83.1		83.1		70.7	
>2.0 ng/ml	53.1		76.3		63.4		52.6	
PET-CT		0.052		0.535		0.060		0.069
No	48.1		76.3		57.8		47.4	
Yes	83.0		83.0		93.3		92.9	
Total radiation dose		0.518		0.972		0.931		0.821
<60 Gy	70.7		81.5		70.7		68.2	
≥60 Gy	58.3		78.6		73.4		55.8	
CR status		<0.001		<0.001		<0.001		<0.001
CR	88.9		94.1		94.4		85.2	
Non-CR	0		42.9		15.6		11.7	

PFS progression-free survival, *LC* local control, *DMFS* distant metastasis-free survival, *OS* overall survival, *FIGO* International Federation of Gynecology and Obstetrics, *SCC Ag* squamous cell carcinoma antigen, *PET-CT* positron emission tomography-computed tomography, *CR* complete response

[a]Survival rate at 5 years (%)

from rectal bleeding and underwent endoscopic intervention 1 year after completing salvage CCRT. Other late toxicities such as hematuria, small bowel obstruction, or vaginal stenosis were not observed.

Treatment response

At the first evaluation within 6 months after salvage treatment, complete response (CR) was achieved in 23 patients (69.7%) and partial response (PR) in 4 patients (12.1%). The univariate logistic regression analysis revealed initial stage (0–FIGO IB1 vs. FIGO IB2–IIA1), pelvic sidewall involvement, and evaluation with PET-CT as important predictive factors for CR (Table 2). In multivariate logistic regression analysis incorporating these factors, pelvic sidewall involvement (hazard ratio [HR], 16.474; 95% confidence interval [CI]I, 1.460–185.895; $p = 0.023$) and evaluation with PET-CT (HR, 0.026; 95% CI, 0.002–0.4463; $p = 0.012$) were significantly associated with CR achievement.

Survival rates

The median follow-up period was 53 months (range, 7 to 158 months) for survivors. During the follow-up period, 11 patients experienced disease progression: local progression in 3 patients, distant metastasis in 5 patients, and both local and distant progression in 3 patients. Of the 23 patients who achieved CR at the first evaluation, 2 patients experienced disease progression (one distant metastasis and one local progression). Disease progression did not occur in any patients treated with RT alone.

Of the patients with disease progression, 8 received palliative chemotherapy and 1 patient received re-irradiation with 24 Gy in 6 fractions, using an intensity-modulated technique. Of these patients, 2 (1 patient treated with palliative chemotherapy and 1 patient treated with re-irradiation) achieved a second CR and survived with no evidence of disease.

Table 4 Multivariate analysis for clinical outcomes

Variables	PFS			LC			DMFS			OS		
	HR		*p*-value	HR	95% CI	*p*-value	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Initial FIGO stage	12.236	1.061–141.088	0.045	–	–	–	11.358	1.235–104.460	0.032	5.277	1.192–23.360	0.028
Pelvic wall involved	20.924	1.368–320.046	0.029	–	–	–	–	–	–	–	–	–
CR status	–	–	–	20.347	2.061–200.923	0.010	50.599	3.654–700.658	0.003	11.431	2.183–59.855	0.004

PFS progression-free survival, *LC* local control, *DMFS* distant metastasis-free survival, *OS* overall survival, *HR* hazard ratio, *CI* confidence interval, *FIGO* International Federation of Gynecology and Obstetrics, *CR* complete response

During the follow-up period, 9 patients died of disease progression and 1 patient died from advanced gastric cancer. The 5-year PFS, LC, DMFS, and OS rates were 62.7, 79.5, 72.5, and 60.1%, respectively (Fig. 2). In the univariate log-rank test, initial stage (0–FIGO IB1 vs. FIGO IB2–IIA1), pelvic sidewall involvement, recurrent tumor size, and CR status were significantly associated with all survival outcomes (Table 3). Young age (<40 years) significantly reduced LC (p = 0.012) and OS (p = 0.043), although its impact had borderline significance on PFS and DMFS. Evaluation with PET-CT prior to initiation of salvage treatments tended to improve PFS (p = 0.060), DMFS (p = 0.052), and OS (p = 0.069). However, disease-free interval, level of SCC-Ag at recurrence and total radiation dose were not significantly associated with any survival rates. Multivariate analysis identified that initial stage significantly infleunced on DMFS, PFS, and OS (Table 4). In addition, while pelvic sidewall involvement significantly reduced PFS, CR status significantly improved LC, DMFS, and OS.

Discussion

The present study demonstrated: 1) encouraging results of salvage RT with or without concurrent chemotherapy, 2) acceptable acute and late toxicities from aggressive local salvage treatments, and 3) initial stage, pelvic sidewall involvement, and CR status as significant prognostic factors.

The present study appeared to show better oncologic outcomes compared with previous literatures (supplementary table 1) [7, 9–12, 16, 17, 21, 23, 24]. An increasing CR rate with aggressive local salvage treatments might be the most important factor for favorable outcomes. Of the 23 patients with CR, only 1 patient experienced distant metastasis, even though none of the patients received maintenance chemotherapy after completion of CCRT or RT. In contrast, distant metastases were found in 7 out of 10 patients without CR. This finding suggested that recurrent cervical cancer confined to the pelvic cavity had a lower risk of systemic dissemination at the time of diagnosis with recurrence. Furthermore, CR status was significantly associated with LC and DMFS rate in the present study. Therefore, aggressive local salvage treatments could be considered as the first-line therapy for elimination of gross tumor and prevention of secondary disseminated spread. This finding was supported by results from previous studies reporting higher CR rates, in which survival rates also tended to be increased.

In addition to aggressive local salvage treatments, careful patient selection with a comprehensive workup prior to treatment could also affect a higher CR rate. The present study demonstrated the impact of PET-CT in the evaluation

of patients with recurrent cervical cancer before initiation of salvage treatments. The current role of PET-CT in recurrent cervical cancer is focused on localization of a suspicious finding and exclusion of distant metastases before local salvage treatments. The present study suggested that evaluation with PET-CT might have the potential to predict treatment response and to influence prognosis for pelvic recurrence of cervical cancer. Therefore, a thorough systemic evaluation with PET-CT at the time of diagnosis with recurrence might be recognized as a prerequisite for identifying suitable patients for successful salvage treatments, and for determining the appropriate radiation field.

In previous studies, the incidence of severe acute hematologic toxicities (≥grade 3) related to CCRT was 6.1–62% [16, 17, 21, 24]. This large variation in the incidence of acute toxicities was associated with the different chemotherapeutic regimens applied and the total numbers of chemotherapy cycles administered. The incidence of severe acute hematologic toxicities in the present study was relatively low (12.1%). This could be elucidated by the inclusion of patients treated with RT alone or weekly cisplatin. Several factors might have been responsible for the low incidence of late gastrointestinal toxicities in the present study (3.3%) compared with previous investigations, including the short follow-up period, the relatively low total radiation dose, and the absence of previous adjuvant treatments.

The results of the present study do not suggest that all patients with pelvic recurrence after hysterectomy alone for early-stage cervical cancer should be indicated for salvage CCRT. Patients with microscopic or small-sized tumors could achieve CR and become long-term survivors with no evidence of disease by RT alone. Ito et al. reported favorable long-term OS of patients treated with RT alone for non-palpable stump recurrence [11]. Therefore, for non-palpable microscopic recurrent cervical cancer, RT alone might be sufficient to control recurrent tumors and expect long-term survival.

In the present study, initial stage was an important prognostic factor for survival outcomes. Jain et al. also reported a similar finding that patients who had undergone simple hysterectomy demonstrated better disease-specific survival than those who had undergone radical hysterectomy [12]. Considering that patients treated with simple hysterectomy had higher possibility of having very early-stage tumors at initial diagnosis, initial stage might significantly influence the outcomes of patients with recurrent cervical cancer. In the present study, initial stage was significantly relevant to pelvic sidewall involvement (27.3% for initial stage 0–FIGO IB1 vs. 70.0% for initial FIGO stage IB2–IIA; $p = 0.049$) and this feature could also influence its prognostic impact.

Although the present study demonstrated that salvage CCRT appeared to improve survival rates for recurrent cervical cancer confined to the pelvic cavity, the prognosis of patients with pelvic sidewall involvement was still disappointing even after salvage CCRT, with a 5-year OS of 29%.Many previous studies have consistently identified pelvic sidewall involvement as a representative of the poor prognostic factors [7, 9, 10, 12, 17]. The poor prognosis of patients with pelvic sidewall involvement might be explained by the difficulty of delivering high radiation doses using vaginal cuff brachytherapy. In addition, pelvic sidewall involvement has increased chances of tumor dissemination via abundant lymphatic pathways. Since the addition of concurrent chemotherapy appeared to play a limited role in the treatment of recurrent cervical cancer with pelvic sidewall involvement, delivering a high radiation dose with large fraction size instead of vaginal cuff brachytherapy or maintenance chemotherapy could be considered.

Hypofractionated or stereotactic body RT (SBRT) has recently emerged as an alternative to brachytherapy in recurrent cervical cancer located at the pelvic sidewall. Guckenberger et al. reported a 3-year LC of 81% for patients with recurrent gynecologic malignancies, including 17 patients with recurrent cervical cancer, who received whole pelvic irradiation followed by a boost with SBRT [8]. However, an unacceptable incidence of late toxicities (25%) was a major concern. Seo et al. also reported a high rate of late toxicities (30%) with SBRT for recurrent cervical cancer with large gross tumor volume at the pelvic sidewall [20]. Therefore, safe delivery of a higher radiation dose with a more precise technique and careful selection of indications should be investigated before active utilization of SBRT, in order to minimize severe toxicities.

Duenas-Gonzalez et al. reported survival improvement in patients with locally advanced cervical cancer who received maintenance chemotherapy after definitive CCRT [4]. However, this trial had several underlying controversies, including inappropriate statistical design and a possible underestimation of late toxicities related to intensified chemotherapy [22]. Therefore, the beneficial role of maintenance chemotherapy should be confirmed by further studies.

Several issues still remain for the treatment of recurrent cervical cancer confined to the pelvic cavity. For example, routine use of elective whole-pelvic irradiation is questionable, although most of the previous studies and the present study have adopted whole-pelvic irradiation [7, 9, 10, 12, 17, 21, 24]. In contrast, Ito et al. demonstrated similar treatment outcomes in patients with non-palpable or small stump recurrence when comparing external beam RT plus brachytherapy versus brachytherapy alone [11]. The current guideline advocates tumor-directed RT, which may include external beam RT, to the pelvis and/or brachytherapy,

leaving room for clinicians' discretion according to circumstances [18]. Besides, total radiation dose, the sequence of chemoradiotherapy and the optimal chemotherapeutic regimen should also be discussed. As long-term survival could be expected in more patients after aggressive salvage RT or CCRT, late toxicities should be monitored continuously for a long time.

The present study has some drawbacks, including its retrospective nature, inherent selection bias, the small number of patients, heterogeneous treatment approaches, and potential recall biases which made it difficult to assess late toxicities.

Conclusion

Nevertheless, the present study showed that long-term survival with no evidence of disease could be achieved by aggressive salvage CCRT or RT in a considerable number of patients with recurrent cervical cancer confined to the pelvic cavity, irrespective of the intensified systemic treatment. In addition, salvage pelvic CCRT or RT showed comparable tolerability. As the results of the present study suggest that pelvic recurrence of cervical cancer comprises a heterogeneous disease with various sizes and extents, treatment strategies should be individualized. In particular, more intensified local and systemic treatments might be required for patients with certain adverse features, including initial FIGO stage IB2–IIA, pelvic sidewall involvement, and non-CR status. Future studies with long-term follow-up are warranted to confirm these results.

Compliance with ethical guidelines

Conflict of interest S.-W. Kim, M. Chun, H.-S. Ryu, S.-J. Chang, T.W. Kong, E.J. Lee, Y.H. Lee, and Y.-T. Oh declare that they have no competing interests.

Ethical standards This study was performed in accordance with the guidelines of the institutional review board, which waived the requirements of informed consent due to the retrospective nature of this study.

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