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The Impact of Histological Subtype on Survival Outcome of Patients with Stage IIB-IVA Cervical Cancer Who Received Definitive Radiotherapy

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The impact of histologic subtype on definitive radiotherapy for patients with locally advanced cervical cancer remains unclear. The aim of this retrospective analysis was to assess clinicopathological findings and clinical outcome by histological type in patients with stage IIB-IVA cervical cancer. Ninety-two patients with stage IIB-IVA [International Federation of Gynecology and Obstetrics (FIGO) 2008] cervical cancer, who underwent definitive radiotherapy between 2013 to 2018, were identified as eligible for this study. The clinical information of the eligible patients was obtained from medical records of our hospital. Seventy-eight patients underwent concurrent chemoradiotherapy, and the remaining 14 patients received radiotherapy alone. Of 92 patients, 83 had squamous cell carcinoma (SCC) and 9 had non-SCC histology. Progression-free survival (PFS) rate of patients with non-SCC was significantly worse than of those with SCC (2-year PFS: 62.0% vs. 12.5%, p = 0.0020), but overall survival (OS) rate did not statistically differ between the two subtypes (2-year OS: 82.4% vs. 62.5%, p = 0.2157). Pelvic failure-free (PFF) rate of patients with non-SCC histology was significantly worse than of those with non-SCC (2-year PFF; 88.2% vs. 25.0%, p < 0.0001). In univariate analysis, non-SCC histology was associated with PFS rate, although there was no association with OS rate. In multivariate analysis, non-SCC histology and lymph node metastasis were independent prognostic factors for shorter PFS. In patients with stage IIB-IVA cervical cancer who underwent definitive radiotherapy, patients with non-SCC showed significantly worse PFS rate than those with SCC.

Keywords: concurrent chemoradiotherapy; histologic type; non-squamous cell carcinoma; uterine cervical neoplasms; radiotherapy
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Introduction

Uterine cervical cancer (UCC) is the fourth most common cancer in women after breast, colorectal, and lung cancer. Approximately 570,000 new cases and 311,000 deaths occurred worldwide in 2018 (Arbyn et al. 2020). Squamous cell carcinoma (SCC) accounts for greater than 70% of all UCC, and adenocarcinoma (AC) and adenosquamous carcinoma (ASC) account for approximately 20% and 3-4%, respectively (Watson et al. 2008). In Japan, of 7,304 women newly diagnosed with UCC in 2018, 2,338 (32.0%) were diagnosed with International Federation of Gynecology and Obstetrics (FIGO 2018) stage IIB-IVA (IIB 1,302, 17.8%; IIIA 105, 1.4%; IIIB 738, 10.1%; IVA 193, 2.6%). With regard to histologic type, SCC was found in 72.8% in Japan, similar to worldwide (Yaegashi 2020).

The National Comprehensive Cancer Network (NCCN) guideline recommended definitive radiotherapy, including concurrent chemoradiotherapy (CCRT) for patients with stage IIB, III, and IVA of UCC regardless of histological type (NCCN 2020). Japan Society of Gynecologic Oncology (JSGO) guidelines also recom-

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mended definitive radiotherapy for patients with stage IIB, III, and IVA of UCC (Ebina et al. 2019). However, radical hysterectomy (RH) has also been recommended for patients with stage IIB disease, especially of non-SCC histology. The difference in surgical methods between Japan and Western countries greatly affects the recommended treatment. In Western country, Wertheim's RH has been employed, while in Japan "the Okabayashi's radical hysterectomy method" was developed for higher curability with wide extirpation of the parametrial tissue and a quite novel finding on separation of the posterior leaf of the vesicouterine ligament (Ebina et al. 2019). A previous randomized study of RH versus radiotherapy in stage IB-IIA UCC showed a significant advantage for RH compared with radiotherapy in patients with AC in the subgroup analysis (Landoni et al. 1997).

A survey of the Japanese Gynecologic Oncology Group (JGOG) reported that CCRT was performed at 53 of 166 institutions (31.9%) for stage IIB SCC disease, but at only 28 institutions (17.0%) for stage IIB non-SCC disease (Mikami et al. 2014), suggesting that there are a certain number of gynecologic oncologists in Japan who believe that non-SCC cervical cancer is less radiosensitive than SCC (Shimada et al. 2020). Indeed, some previous studies showed that UCC of non-SCC histology was more resistant to radiotherapy and more aggressive, and that local control rate was poor in non-SCC (Katanyoo et al. 2012; Yokoi et al. 2017). In contrast, Rose et al. (2014) reported that UCC of non-SCC histology was associated with worse overall survival (OS) rate when treated with radiation alone, but had similar progression-free survival (PFS) and OS rate compared to UCC of SCC histology when treated with CCRT.

Thus, the association between histological subtypes and radiosensitivity in definitive radiotherapy for locally advanced cervical cancer is controversial. We conducted this retrospective study to assess differences of clinical outcome by histological subtype.

Methods

Patients

The study was approved by the institutional Review Board of Tohoku University Hospital (Reception Number 2021-1-1178). Informed consent was obtained in the form of opt-out on the web-site. Medical records of stage IIB-IVA (FIGO 2008) cervical cancer patients treated with definitive radiotherapy (included CCRT) in our institute from 2013 to 2018 were reviewed. The eligibility criteria were cervical cancer with a definitive diagnosis of histological subtype in biopsy specimens.

Treatment

Patients who had complications for chemotherapy or who were aged > 75 years received radiotherapy alone without concurrent chemotherapy. External beam radiotherapy (EBRT) plus high dose rate (HDR) brachytherapy was performed in our standard protocol.

Regarding EBRT, many patients received a combination of whole pelvic (WP) irradiation and center shield (CS) irradiation including the prophylactic regions with a dose of 45 to 50.4 Gy. Clinical target volume at WP irradiation included the whole uterus, parametrium, vagina, ovary, and the regional lymph node regions (internal iliac, external iliac, common iliac, and presacral lymph nodes). The para-aortic lymph node region was also included in the radiation field if para-aortic lymph node metastasis was detected at initial diagnosis. CS irradiation with a 4-cm-wide block was switched after WP with a dose of 20 to 40 Gy to reduce the dose to the rectum and bladder. The start time of CS was determined upon tumor response during CCRT and tumor size at initial diagnosis by radiation oncologists. For patients with lymph node metastasis, nodal boost irradiation with a dose of 6 to 10 Gy was delivered after WP or CS. Fractionated doses of 1.8 to 2.0 Gy in EBRT were delivered 5 days a week.

HDR brachytherapy mainly as intracavity brachytherapy (ICBT) was delivered using an iridium-192 remote after loading system within 1 week with after WP. HDR brachytherapy was performed once or twice per week, for a total of 2-4 fractions. Either tandem/ovoid or tandem/cylinder applicators were used in ICBT. In patients with large or irregular shaped tumors, hybrid brachytherapy (HBT) by means of a combination of ICBT and interstitial brachytherapy has been performed since 2017, and additional needle catheters were inserted in combination with ICBT applicators. In principle, the prescription dose per fraction at HDR brachytherapy was 6 Gy at point A using the Manchester method. As needed, dose distribution was adjusted by manual modification to cover the primary tumor and reduce the dose to the rectum and bladder.

Concurrent chemotherapy regimen was fundamentally weekly platinum-based chemotherapy [cisplatin (CDDP) or nedaplatin (NDP)]. The routine regimen was CDDP at a dose of 40 mg/m^2. Patients with worse tolerability for CDDP were treated by NDP at a dose of 30 mg/m^2. NDP, a CDDP analog, has been developed to decrease the toxicities induced by CDDP, such as nephrotoxicity (Shimada et al. 2013).

Patient follow-up

Patients who had complete treatment had regular follow-up with cervical smears, ultrasonography, and serum tumor markers, generally once every 2-3 months in the first year, every 3-4 months in the second and third year, and every 6 months thereafter. Chest/abdomen computerized tomography (CT) was usually performed every 6 months. Positron emission tomography (PET) was occasionally performed when CT could not sufficiently reveal disease condition. Patients whose disease did not progress after five years were referred to another gynecological clinic for further follow-up.

Assessment of treatment outcomes

The endpoints included PFS, OS, pelvic failure-free (PFF), distant metastasis-free (DMF), and complete response (CR) rates. PFS was defined as the time from start of treatment to date of disease progression on imaging such as CT or PET, and OS as the time from start of treatment to the time of death from cervical cancer. Pelvic failure free was defined as no progression intra pelvis containing vaginal stump, pelvic lymph node and dissemination. CR was defined as no residual carcinoma on cervical biopsy, shrinkage of tumor, and no new lesions on imaging. Grade 3 or more late toxicities of radiation were extracted from medical records and assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 translated by the Japanese Clinical Oncology Group (CTCAE v5.0 -JCOG).

Statistics

Survival analysis was calculated using the Kaplan-Meier method. The significance of the survival distribution was assessed by log-rank test. Student's t-test and the chi-squared test were used for comparing two groups. Cox proportional hazard regression analysis was carried out to identify independent predictors of survival. P-values of < 0.05 were considered to be statistically significant. All analyses were performed using the software JMP Pro, version14.3.0 (SAS Institute, Cary, NC, USA).

Results

Ninety-two patients with stage IIB, III and IVA of UCC (SCC: 83, non-SCC: 9) were eligible to be included in this retrospective study. Those with non-SCC histology included 8 with AC and 1 with ASC. Patients' characteristics are shown in Table 1. There were 60 patients with stage IIB, 25 with stage III, and 7 with stage IVA. Seventy-eight patients underwent CCRT and the remaining 14 patients received radiotherapy alone. In the CCRT regimen, 67 patients were treated with CDDP, 9 patients received NDP, 1 patient received carboplatin (CBDCA) and paclitaxel (PTX), and 1 patient received CDDP and PTX.

The CR rate to treatment for patients with SCC and non-SCC was 88.0% and 66.7%, respectively ($p = 0.063$) (Table 2). Nine patients with SCC histology and 2 with non-SCC histology unfortunately did not have CR to treatment. Of 9 patients with SCC histology who did not have CR, 8 patients had new distant metastasis or para-aortic lymph node metastasis outside the irradiation field while undergoing definitive radiotherapy. The remaining patient had a buttocks tumor before treatment, which had only partial response to CCRT. Two patients of non-SCC histology who did not achieve CR had distant or para-aortic lymph node metastasis during treatment.

Table 3 shows the progression field according to histologic subtype. The first progression field did not differ between patients with SCC and those with non-SCC histology. In the SCC group, 35 patients had disease progression, including 4 (11.4%) who progressed in the irradiation field, 25 (71.4%) who progressed outside of the irradiation field, and 6 (17.1%) who progressed both inside and outside the irradiation field. In the non-SCC group, of 7 patients with disease progression, 3 (42.9%) progressed in the irradiation field, 3 (42.9%) progressed outside of the irradiation field, and 1 (14.3%) progressed both inside and outside the irradiation field.

In those who progressed within the pelvic region, of 10 patients with SCC histology, one patient had local recurrence and 5 patients had recurrence in pelvic lymph node. The others had recurrence in another part such as peritoneal dissemination. Of 4 pelvic patients with non-SCC histology, no patient had local recurrence and 1 patient had recurrence in the pelvic lymph node. The others had recurrence in another part. There was no association between area of recurrence and non-SCC histology.

Median follow-up time was 40 months (range, 4-77 months) in SCC and 15 months (range, 1-59 months) in non-SCC. The PFS rate of patients with non-SCC was significantly worse than that of patients with SCC (2-year PFS, 62.0% vs. 12.5%, $p = 0.0020$) (Fig. 1A), although there was no significant difference in OS rate between SCC and non-SCC (2-year OS, 82.4% vs. 62.5%, $p = 0.2157$) (Fig. 1B). The PFF rate of patients with non-SCC was significantly worse than that of patients with SCC (2-year PFF, 88.3% vs. 25.0%, $p < 0.0001$) (Fig. 1C). The DMF rate was not different between the two subtypes (2-year DMF, 66.4% vs. 33.3%, $p = 0.1206$) (Fig. 1D).

In univariate analysis, non-SCC histology was associated with worse PFS rate, although there was no significant association for OS rate. Patient age, FIGO stage, tumor size, lymph node metastasis, treatment (RT with or without concurrent chemotherapy), and type of brachytherapy did not make a difference in PFS and OS rates (Table 4). Multivariate analysis revealed that non-SCC histology [hazard ratio (HR), 5.00; 95% confidence interval (CI), 1.85 to 13.54; $p = 0.002$] and lymph node metastasis (HR, 2.20; 95% CI, 1.06 to 4.55; $p = 0.034$) were independent prognostic factors for PFS rate. Treatment with RT alone (HR, 4.40; 95% CI, 1.37 to 14.17; $p = 0.013$) was an independent factor for OS rate, although there was no significant association with PFS rate (Table 5).

Details of patients with non-SCC histology are shown in the Table 6. Six of 9 patients with non-SCC histology were human papillomavirus (HPV)-associated adenocarcinoma, and histological types classified as HPV-independent (WHO 2020) were not included. Seven of 9 patients had progressed disease or recurrence, including 2 cases of peritoneal dissemination, 2 cases of pulmonary metastasis, and 2 cases of lymph node metastasis, after definitive radiotherapy. Patient No.3 disappeared after treatment, and we could not get in touch with her.

Grade 3 late toxicities occurred in 10 patients (10/92; 10.8%), including 9 of SCC patients and 1 of non-SCC patients. In 9 patients with SCC, 7 patients had enteritis,

Table 1. Patient's characteristics.

	All (n = 92)	SCC (n = 83)	non-SCC (n = 9)	P-value
Median follow-up period (months)	39 (1-77)	40 (4-77)	15 (1-59)	0.016
Median age (years)	55 (30-84)	55 (30-84)	62 (45-78)	0.130
Age (years)				0.303
< 50	35 (38.0%)	33 (39.8%)	2 (22.2%)	
50 ≦	57 (62.0%)	50 (60.2%)	7 (77.8%)	
FIGO 2008 stage				0.161
IIB	60 (65.2%)	56 (67.5%)	4 (44.4%)	
IIIA,IIIB	25 (27.2%)	20 (24.1%)	5 (55.6%)	
IVA	7 (7.6%)	7 (8.4%)	0	
Tumor size (cm)				0.063
< 4	19 (20.7%)	15 (18.1%)	4 (44.4%)	
4 ≦	73 (79.3%)	68 (81.9%)	5 (55.6%)	
Treatment				0.622
CCRT	78 (84.8%)	71 (85.5%)	7 (77.8%)	
RT alone	14 (15.2%)	12 (14.5%)	2 (22.2%)	
Brachytherapy				0.457
ICBT alone	73 (79.3%)	65 (78.3%)	8 (88.9%)	
HBT	19 (20.7%)	18 (21.7%)	1 (11.1%)	
Lymph node metastasis				
PLN or PAN metastasis				0.785
Yes	55	50	5	
No	37	33	4	
PLN metastasis only				0.732
Yes	44 (47.8%)	39 (47.0%)	5 (55.6%)	
No	48 (52.2%)	44 (53.0%)	4 (44.4%)	
PLN plus PAN metastasis				0.600
Yes	12 (13.0%)	12 (14.5%)	0	
No	80 (87.0%)	71 (85.5%)	9 (100%)	

Data are shown as median (range) or n (%).
SCC, squamous cell carcinoma; non-SCC, non squamous cell carcinoma; FIGO, International Federation of Gynecology and Obstetrics; CCRT, concurrent chemoradiotherapy; RT, radiotherapy; ICBT, Intracavitary brachytherapy; HBT, hybrid brachytherapy; PLN, pelvic lymph node; PAN, para-aortic lymph node.

Table 2. Response to treatment according to histologic subtype.

	All (n = 92)	SCC (n = 83)	non-SCC (n = 9)	P-value
CR	79 (85.9%)	73 (88.0%)	6 (66.7%)	0.063
not CR	11 (12.0%)	9 (10.8%)	2 (22.2%)	
NA	2 (1.1%)	1 (1.2%)	1 (11.1%)	

Data are shown as n (%).
SCC, squamous cell carcinoma; non-SCC, non squamous cell carcinoma; CR, complete response; NA, not available.

Table 3. Progression field according to histologic subtype.

	All (n = 42)	SCC (n = 35)	non-SCC (n = 7)	P-value
				0.152
Irradiation field	7 (16.7%)	4 (11.4%)	3 (42.9%)	
Outside of irradiation field	28 (66.7%)	25 (71.4%)	3 (42.9%)	
Both	7 (16.7%)	6 (17.1%)	1 (14.3%)	

Data are shown as n (%).
SCC, squamous cell carcinoma; non-SCC, non squamous cell carcinoma.

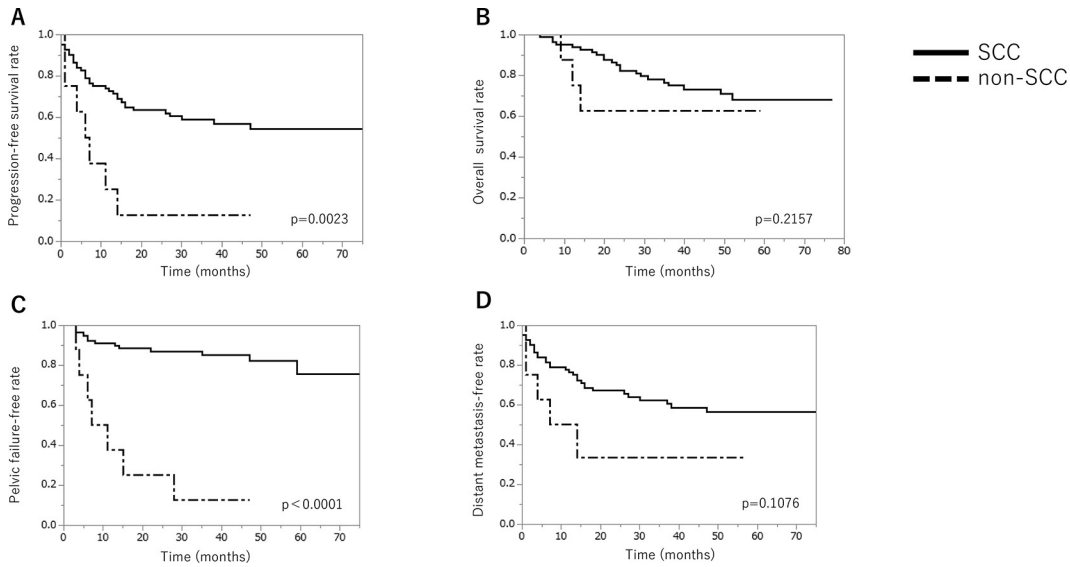

Fig. 1. Survival outcome by histological subtype in patients who underwent definitive radiotherapy.
A) Progression-free survival (PFS) by histological subtype. The 2-year PFS rate for patients with non-SCC was significantly worse than for those with SCC (SCC vs. non-SCC: 2-year PFS; 62.0% vs. 12.5%, p = 0.0020). B) Overall survival (OS) rate by histological subtype. The 2-year OS rate was not significantly different between SCC and non-SCC. (SCC vs. non-SCC: 2-year OS; 82.4% vs. 62.5%, p = 0.2157). C) Pelvic failure-free (PFF) rate by histological subtype. The 2-year PFF rate for patients with non-SCC were significantly worse than for those with SCC (SCC vs. non-SCC: 2-year PFF; 88.3% vs. 25.0%, p < 0.0001). D) Distant metastasis-free (DMF) rate by histological subtype. The 2-year DMF rate was not significantly different between the two histological subtypes (SCC vs. non-SCC: 2-year DMF; 66.4% vs. 33.3%, p = 0.1206)

and 2 patients had bladder tamponade caused by cystitis noninfective and hematuria. Of 7 patients with enteritis, 3 patients had surgery because of ileal obstruction (2 patients) and ileal perforation (1 patient). Three patients had hyperbaric oxygen therapy and 1 patient had argon plasma coagulation for rectal hemorrhage. Of two patients with bladder tamponade, one patient had surgery and the other patient had hyperbaric oxygen therapy. One patient with non-SCC had surgery because of colonic perforation.

Discussion

This study found that patients with non-SCC histology of UCC had poorer PFS and PFF rates than those with SCC histology in treatment with radiotherapy. In multivariate analysis, non-SCC histology and lymph node metastasis were independent factors for worse PFS rate. Treatment with radiotherapy alone was associated with worse OS rate.

Some previous studies have also suggested that non-SCC histology had poor prognosis. We summarized previous retrospective studies by histological type of definitive radiation therapy including CCRT for locally advanced cervical cancer in Table 7. Although histological type was commonly shown to be a poor prognostic factor in univariate analysis, few multivariate analyses showed similar results for PFS and OS. Hu et al. (2018) investigated 815 patients with stage IB-IVA UCC treated with definitive radiotherapy or CCRT, included 744 patients with SCC and 71 patients with AC. The 3-year OS, disease-free survival (DFS), pelvic control, and distant control rates of patients with AC were significantly worse than SCC. In multivariate analysis, AC histology was an independent factor of OS (p = 0.003), DFS (p < 0.001), pelvic control (p = 0.002), and distant control (p = 0.003) rates. Their study also confirmed that tumor size and FIGO stage were poor prognostic factors after multivariate analysis. Yokoi et al. (2017) investigated 249 patients with FIGO stage IIB-IVA cervical

Table 4. Univariate analysis of prognostic factors.

Variables	PFS		OS	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (years)				
< 50	1.00 (reference)	–	1.00 (reference)	–
50 ≦	0.87 (0.48-1.60)	0.647	0.74 (0.34-1.64)	0.462
Histology				
SCC	1.00 (reference)	–	1.00 (reference)	–
non-SCC	3.16 (1.39-7.22)	0.006	2.11 (0.63-7.10)	0.228
Stage (FIGO2008)				
IIB	1.00 (reference)	–	1.00 (reference)	–
IIIA, IIIB	1.49 (0.76-2.93)	0.247	1.66 (0.70-3.97)	0.253
IVA	2.24 (0.85-5.88)	0.102	2.64 (0.75-9.28)	0.130
Tumor size (cm)				
< 4	1.00 (reference)	–	1.00 (reference)	–
4 ≦	1.59 (0.67-3.78)	0.293	1.05 (0.39-2.80)	0.926
PLN or PAN metastasis				
Negative	1.00 (reference)	–	1.00 (reference)	–
Positive	1.90 (0.97-3.71)	0.061	1.58 (0.68-3.65)	0.290
PLN metastasis				
Negative	1.00 (reference)	–	1.00 (reference)	–
Positive	1.58 (0.86-2.92)	0.141	1.52 (0.69-3.35)	0.300
PLN and PAN metastasis				
Negative	1.00 (reference)	–	1.00 (reference)	–
Positive	1.57 (0.70-3.54)	0.276	1.33 (0.46-3.89)	0.602
Treatment				
CCRT	1.00 (reference)	–	1.00 (reference)	–
RT alone	1.82 (0.84-3.94)	0.127	2.70 (1.13-6.47)	0.026
Brachytherapy				
ICBT alone	1.00 (reference)	–	1.00 (reference)	–
HBT	1.14 (0.54-2.38)	0.735	1.31 (0.48-3.56)	0.591

PFS, progression free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; SCC, squamous cell carcinoma; non-SCC, non squamous cell carcinoma; FIGO, International Federation of Gynecology and Obstetrics; PLN, pelvic lymph node; PAN, para-aortic lymph node; CCRT, concurrent chemoradiotherapy; RT, radiotherapy; ICBT, Image-based intracavitary brachytherapy; HBT, hybrid brachytherapy.

cancer (SCC: 225, AC/ASC: 24) retrospectively. The patients with AC/ASC exhibited significantly worse OS and PFS rates than those with SCC. Multivariate analysis showed that AC/ASC histology was an independent negative prognostic factor for PFS rate. In their multivariate analysis, age, FIGO stage, pelvic lymph node metastasis, and tumor size did not affect PFS rate in all histology. Chen et al. (2014) compared tumor characteristics and clinical outcome of patients with SCC (n = 194) and AC or ASC (n = 35) histology of locally advanced UCC. In analysis with the Kaplan-Meier method, patients with AC/ASC had worse 5-year PFS (p = 0.044) and worse 5-year DMF (p = 0.005) rates than patients with SCC histology. In multivariate analysis, instead of histologic difference, complete treat-

Table 5. Multivariate analysis of prognostic factors.

Variables	PFS		OS	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age				
< 50	1.00 (reference)	–	1.00 (reference)	–
50 ≦	0.64 (0.32-1.27)	0.205	0.46 (0.18-1.18)	0.106
Histology				
SCC	1.00 (reference)	–	1.00 (reference)	–
non-SCC	4.70 (1.76-12.55)	0.002	2.89 (0.71-11.76)	0.139
FIGO 2008 stage				
IIB	1.00 (reference)	–	1.00 (reference)	–
IIIA,IIIB	0.86 (0.39-1.91)	0.708	0.87 (0.29-2.56)	0.795
IVA	1.89 (0.70-5.09)	0.207	2.33 (0.64-8.49)	0.200
Tumor size (cm)				
< 4	1.00 (reference)	–	1.00 (reference)	–
4 ≦	1.47 (0.69-3.59)	0.397	0.93 (0.34-2.55)	0.890
LN (PLN or PAN) metastasis				
Negative	1.00 (reference)	–	1.00 (reference)	–
Positive	2.18 (1.04-4.53)	0.037	1.86 (0.74-4.68)	0.190
Treatment				
CCRT	1.00 (reference)	–	1.00 (reference)	–
RT	2.08 (0.81-5.30)	0.127	4.40 (1.37-14.17)	0.013

PFS, progression free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; SCC, squamous cell carcinoma; non-SCC, non squamous cell carcinoma; FIGO, International Federation of Gynecology and Obstetrics; PLN, pelvic lymph node; PAN, para-aortic lymph node; CCRT, concurrent chemoradiotherapy; RT, radiotherapy.

ment response and early stage remained significant factors for PFS and OS rates, but complete treatment response rate was lower in AC/ASC histology than in SCC (p = 0.018). In accordance with previous studies, we demonstrated poor prognosis of patients with non-SCC histology with locally advanced UCC. However, tumor size and FIGO stage had no significant relationship to poor PFS or OS rates in the present study. In previous studies, there were some differences in clinicopathological findings, including stage, presence of lymph node metastasis, and chemotherapeutic agents using at CCRT, which may have caused differences in the results of this study.

With the revision of FIGO (2018) staging system, in addition to "stage IIICp" based on pathological diagnosis, "stage IIICr" based on radiological diagnosis was newly established as stage IIIC, and lymph node metastasis, which was pointed out as an independent prognostic factor, was adopted as the defining factor for FIGO (2018) staging system. In the present study, lymph node metastasis was an independent poor prognostic factor for worse PFS in multivariate analysis, which was not revealed in previous studies.

Although many authors reported the worse prognosis of non-SCC histology, no new therapeutic methods have been established to improve the outcome of patients. The results of the current study suggest that how to control the lesions outside of irradiation field might be a critical point in patients with non-SCC. Duenas-Gonzalez et al. (2011) reported the result of phase III study comparing CCRT and CCRT followed by adjuvant chemotherapy using CDDP and gemcitabine for 515 patients with stage IIB to IVA UCC. CCRT followed by adjuvant chemotherapy significantly improved both PFS and OC in stage IIB-IVA patients with UCC compared to CCRT. However, CCRT followed by adjuvant chemotherapy showed more frequent grade 3/4 toxicities than those with CCRT alone. There is no analysis by histological type, probably because the proportion of adenocarcinoma is relatively small. Most recently OUTBACK trial, which conducted to determine the effects of adjuvant chemotherapy with 4 cycles of PTX/CBDCA

Table 6. Clinical fetures of non-SCC patients.

Patient No.	Age	Stage (FIGO2008)	Histologic subtype (at the time of diagnosis)	Histologic subtype (WHO2020)	Tumor size (mm)	LN metastasis	Treatment	Response to treatment	Refractory/ recurrence	Recurrent site	PFS (months)	OS (months)	Outcome
1	62	IIB	mucinous adenocarcinoma, endocervical type (WHO2003)	Adenocarcinoma, HPV-associated	45	—	CCRT (CDDP)	CR	+	ovary metastasis	7	15	non-specific death
2	60	IIB	unclassifiable	Adenocarcinoma, NOS	40	—	CCRT (CDDP)	CR	+	lung metastasis	16	38	alive with disease
3	78	IIB	endometrioid adenocarcinoma, G3 (WHO2003)	Endometrioid adenocarcinoma NOS	38	+(PLN)	RT	N/A #1	N/A #1	N/A #1	1	1	alive with disease
4	53	IIIB	mucinous adenocarcinoma, endocervical type (WHO2003)	Adenocarcinoma, HPV-associated	50	+(PLN)	CCRT (PTX+CDDP)	CR	+	peritoneal dissemination	13	59	alive with disease
5	64	IIIB	mucinous adenocarcinoma, endocervical type (WHO2003)	Adenocarcinoma, HPV-associated	30	+(PLN)	CCRT (CDDP)	CR	+	peritoneal dissemination	8	14	disease specific death
6	71	IIIB	mucinous adenocarcinoma, endocervical type (WHO2003)	Adenocarcinoma, HPV-associated	63	—	RT	CR	—	N/A	49	49	disease-free survival
7	70	IIIB	mucinous adenocarcinoma (NOS) (WHO2003)	Adenocarcinoma, HPV-associated	16	+(PLN)	CCRT (CDDP)	CR	+	multiple lymph node metastasis	5	12	disease specific death
8	48	IIIB	mucinous adenocarcinoma (NOS) (WHO2014)	Adenocarcinoma, HPV-associated	28	+(PLN)	CCRT (NDP)	PD	+	para aortic lymph node metastasis	3	18	alive with disease
9	45	IIB	adenosquamous carcinoma (WHO2003)	Adenosquamous carcinoma	54	—	CCRT (CDDP)	PD	+	lung metastasis	2	9	disease specific death

non-SCC, non squamous cell carcinoma; AC, adenocarcinoma; FIGO, International Federation of Gynecology and Obstetrics; HPV, human papillomavirus; NOS, not otherwise specified; LN, lymph node; PLN, pelvic lymph node; CCRT, concurrent chemoradiotherapy; RT, radiotherapy; CDDP, cisplatin; NDP, nedaplatin; PTX, paclitaxel; CR, complete response; PD, progressive disease; PFS, progression-free survival; OS, overall survival.
N/A#1. She disappeared after the treatment, so we could not check on her progress.

Table 7. Studies of definitive radiotherapy for SCC and non-SCC in patients with cervical cancer.

Author	No. of patients		FIGO stage				Treatment					PFS		P-value	OS		P-value
	SCC (%)	non-SCC (%)		Total (%)	SCC (%)	non-SCC (%)	Rejimen		Total (%)	SCC (%)	non-SCC (%)	HR (95 % CI)			HR (95 % CI)		
Hu et al. (2018)	744 (91.3)	71 (8.7)	I	99 (12.1)	92 (92.9)	7 (7.1)	CCRT	CDDP, PTX, CDDP+PTX	673 (82.6)	613 (91.1)	60 (8.9)	SCC	1 (reference)		SCC	1 (reference)	
			II	559 (68.6)	505 (90.3)	54 (9.7)	RT		142 (17.4)	131 (92.3)	11 (7.7)	non-SCC	2.21 (1.49 - 3.25)	< 0.001	non-SCC	2.01 (1.22 - 3.31)	0.006
			III-IVA	157 (19.3)	147 (93.6)	10 (6.4)											
Yokoi et al. (2017)	225 (90.4)	24 (9.6)	IIB	96 (38.6)	81 (84.4)	15 (15.6)	CCRT	NDP	110 (44.2)	96 (87.3)	14 (12.7)	SCC	1 (reference)		SCC	1 (reference)	
			IIIA	12 (4.8)	11 (91.6)	1 (8.3)	RT		139 (55.8)	129 (92.8)	10 (7.2)	non-SCC	1.94 (1.07 - 3.35)	0.031	non-SCC	N/A	
			IIIB	124 (49.8)	118 (95.2)	6 (4.8)											
			IVA	17 (6.8)	15 (88.2)	2 (11.8)											
Rose et al. (2014)	1489 (89.2)	182 (10.8)	IB2	348 (20.8)	298 (85.6)	50 (14.4)	CCRT	5-FU, HU, CDDP, CDDP+5-FU, CDDP+5FU+HU	1472 (88.1)	1316 (89.4)	156 (10.6)	SCC	1 (reference)		SCC	1 (reference)	
			IIB	788 (47.2)	702 (89.1)	86 (10.9)	RT		199 (11.9)	173 (86.9)	26 (13.1)	non-SCC	1.21 (0.98 - 1.51)	0.083	non-SCC	1.25 (1.00 - 1.56)	0.0499
			IIIA	23 (1.4)	20 (87.0)	3 (13.0)											
			IIIB	465 (27.8)	426 (91.6)	39 (8.4)											
			IVA	47 (2.8)	43 (91.5)	4 (8.5)											
Chen et al. (2013)	194 (84.7)	35 (15.3)	IIB	160 (69.9)	134 (83.8)	26 (16.3)	CCRT	CDDP	130 (56.8)	109 (83.8)	21 (16.2)	SCC	1 (reference)		SCC	1 (reference)	
			IIIA, IIIB	56 (24.5)	50 (89.3)	6 (10.7)	RT		99 (43.2)	85 (85.9)	14 (14.1)	non-SCC	1.13 (0.72 - 1.78)	0.600	non-SCC	1.20 (0.73 - 1.95)	0.476
			IVA	13 (5.7)	10 (76.9)	3 (23.1)											
Katanyoo et al. (2012)	282 (66.7)	141 (33.3)	IIB	255 (60.3)	170 (66.7)	85 (33.3)	CCRT	CDDP, CBDCA, CBDCA+5-FU	155 (36.6)	102 (65.8)	53 (34.2)	SCC	1 (reference)		SCC	1 (reference)	
			IIIB	165 (39.0)	110 (66.7)	55 (33.3)	RT		268 (63.4)	180 (67.2)	88 (32.8)	non-SCC	N/A		non-SCC	IIB: 1.13 (0.74 - 1.72)	0.568
			IVA	3 (0.7)	2 (66.7)	1 (33.3)										IIIB/IVA: 1.35 (0.91 - 2.01)	0.139
The present study	83 (90.2)	9 (9.8)	IIB	60 (65.2)	56 (93.3)	4 (6.7)	CCRT	CDDP, NDP, PTX+CDDP	78 (84.8)	71 (91.0)	7 (9.0)	SCC	1 (reference)		SCC	1 (reference)	
			IIIA, IIIB	25 (27.2)	20 (20.0)	5 (20.0)	RT		14 (15.2)	12 (85.7)	2 (14.3)	non-SCC	4.70 (1.76 - 12.55)	0.002	non-SCC	2.89 (0.71 - 11.76)	0.139
			IVA	7 (7.6)	7 (100.0)	0 (0)											

SCC, squamous cell carcinoma; non-SCC, non squamous cell carcinoma; FIGO, International Federation of Gynecology and Obstetrics; CCRT, concurrent chemoradiotherapy; RT, radiotherapy; CDDP, cisplatin; NDP, nedaplatin; PTX, paclitaxel; 5-FU, 5-fluorouracil; HU, hydroxyurea; CBDCA, carboplatin; PFS, progression-free survival; OS, overall survival.

combination chemotherapy after standard CCRT with CDDP on survival compared with CCRT alone, revealed that OS of both groups had no significant difference (Linda R. Mileshkin et al., American Society Annual Meeting 2021, https://meetinglibrary.asco.org/record/196619/abstract). It is still unclear that these results can be adopted for non-SCC.

Recently, efficacy of CCRT with taxane or following taxane chemotherapy for AC has been reported by various authors. Nagai et al. (2012) showed that CCRT with paclitaxel and cisplatin achieved better local control for AC than cisplatin alone. Thirty-two stage IIB-IVA (FIGO 1994) AC patients of uterine cervix enrolled the study and 8 patients received CCRT with cisplatin and 10 patients received with paclitaxel and cisplatin. The 5-year OS rate in the radiotherapy only, CCRT with cisplatin, and CCRT with paclitaxel and cisplatin groups was 7.1%, 25.0%, and 74.1%, respectively ($p = 0.0094$). Their study found that CCRT with paclitaxel and cisplatin regimen contributed to better local control for AC of uterine cervix. Umayahara et al. (2016) reported CCRT with weekly cisplatin (30 mg/m^2) and paclitaxel (50 mg/m^2) brought good prognosis for FIGO stage III-IVA UCC without para-aortic lymphadenopathy. Fifty-seven patients with SCC histology, 4 patients with ASC histology, and 7 patients with AC histology were enrolled in their study, though histologic subtype had no appreciable effect on any of outcome rate. As in these reports, CCRT with taxane regimen for AC will be expected to have a favorable prognosis. Tang et al. (2012) reported that incorporating neo-adjuvant and consolidation chemotherapy with paclitaxel and cisplatin into radiotherapy was effective for advanced cervical adenocarcinoma. In their study, 880 patients with stage IIB-IVA uterine cervical adenocarcinoma were randomized to receive either CCRT alone or CCRT plus neo-adjuvant and adjuvant chemotherapy with paclitaxel and cisplatin. Patients who received adjuvant chemotherapy showed significant good prognosis. Referring further to taxanes, there is a report suggesting that docetaxel (DTX) has some positive effect on non-SCC. Sato et al. (2016) assigned 37 patients with high-risk patients with stage IB-IIB non-SCC to PTX+CBDCA (22 patients) and to DTX+CBDCA (15 patients) for adjuvant chemotherapy after radical hysterectomy. Although there was no significant difference between the two groups, 2-year PFS was 80% in the DC group and 50% in the TC group ($p = 0.1400$).

Furthermore, the effectiveness of carbon iron radiotherapy (C-ion RT) for locally advanced adenocarcinoma of UCC was reported. Fifty-eight patients with stage IB, IIIA, and IVA adenocarcinoma of UCC enrolled in a phase 1/2 clinical trial and treated with C-ion RT without severe toxicities except 1 case. That study showed a 5-year local control and OS rate of 54.5% and 38.1%, respectively. The control rate was relatively better than in conventional studies (Wakatsuki et al. 2014). In recent years, maintenance therapy with molecular targeted agents has also received attention for patients with locally advanced UCC (Lorusso et al. 2020; Mayadev et al. 2020; Toyoshima et al. 2021). Pembrolizumab and durvalmab are PD-L1 inhibitors, and Phase III studies to determine the efficacy and safety of each PD-L1 inhibitor in combination with and following chemoradiotherapy for treatment have been conducted (Lorusso et al. 2020; Mayadev et al. 2020).

The WHO 2020 classification was published, and cervical cancer histology was divided into HPV-associated and HPV-independent. In current study, the histological diagnosis was re-evaluated by the WHO 2020 classification. “Adenocarcinoma, HPV-associated” is defined as a glandular tumor with stromal invasion and/or exophytic expansile-type invasion, associated with high-risk HPV infection. HPV-associated histology includes “endocervival carcinoma, usual type” and ”mucinous carcinoma [intestinal type, signet-ring cell type, not otherwise specified (NOS)]” which had classified in WHO 2014. “Adenocarcinoma, HPV-independent” which has considered to be more aggressive than HPV-associated, are classified into “gastric type”, “clear cell type”, and “mesonephric type”. “Endometrioid carcinoma” in WHO 2014 is also classified as “Endometrioid adenocarcinoma NOS” in WHO 2020. Endometrioid adenocarcinoma has no HPV-related classification, though typically it is independent of HPV. Both “mucinous carcinoma, endocervical type” and “mucinous carcinoma, NOS” in WHO 2003 are classified as “Adenocarcinoma, HPV-associated”.

Machida et al. (2020) evaluated survival outcome in patients with cervical adenocarcinoma subtype by two groupings as follows: type 1 (endocervical usual type and endometrioid) and type 2 (serous, clear, mucinous, and not otherwise specified), using the JSOG database. They reported that patients with type 2 adenocarcinoma showed significantly worse survival than those with SCC. Minimal deviation adenocarcinoma (MDA) is classified in well differentiated gastric-type mucinous adenocarcinoma (GAS) and reported to be refractory to treatment and its prognosis is extremely poor (Kojima. et al. 2007). The causes are reported to be treatment resistance, such as aggressive clinical behavior, low sensitivity to chemotherapy, and low sensitivity to radiation (Li et al. 2010; Lee et al. 2018; Nishio et al. 2019). Previous reports showed that early diagnosis was important to manage. Li et al. (2010) showed that the mean survival was about 5 years for patients with stage I, 38.1 months for patients with stage II, 22.8 months for patients with stage III, and 5.4 months for patients with stage IV MDA. Lee et al. (2018) also reported that advanced stage disease continued to show a significant association with poor OS rate. In a sub-analysis of a phase II study of neoadjuvant chemotherapy for UCC, GAS showed lower chemosensitivity compared to usual type endocervical carcinoma (Kojima et al. 2018). The JCOG conducted a retrospective study of 328 patients with stage I-II endometrial adenocarcinoma of the cervix and reported that the response rate to GAS in 12 patients with additional

postoperative radiotherapy was 50.0% (6/12), whereas the response rate to usual type endocervical adenocarcinoma (UEA) was 81.8% (9/11, p = 0.0001). These results suggested that GAS showed less radiosensitivity compared to UEA (Nishio et al. 2019).

This study does not include patients with HPV-independent subtype (WHO 2020) as represented by MDA. However, this study included 2 patients (No. 7 and No. 8) with mucinous carcinoma (NOS), which was classified type 2 group histology of Machida et al. (2020). Those patients had shown new lesions and disease progression early after initial treatment, which may be a characteristic of type 2 adenocarcinoma. On the contrary, in 9 of non-SCC patients, only one patient (No. 6) has apparently progressed without recurrence. Patient No. 6 was treated with radiation alone because she had a severe infection caused by pyometra at the start of treatment. Furthermore, she had the largest tumor among non-SCC patients at 63 mm. Despite these unfavorable conditions, she has progressed without recurrence. Histology of patients No.6 was classified HPV-associated (WHO 2020) and type1 by Machida's criteria. In contrast, two patients (No. 4 and No. 5) with the exact same histological type had recurrence, so it was difficult to conclude. Although we would like to discuss more about the prognostic differences by histological subtype, small sample size made it impossible in present study.

There are some limitations to our study. The present study was conducted at a single institution and its sample size was small. Additionally, various biases were likely to have affected the results. In particular, the number of patients with AC was only 9 and this small sample size made it impossible to analyze the prognosis of subtypes of non-SCC histology. Furthermore, the median follow-up of non-SCC patients was short (15 months), which may be the main reason why there was no significant difference in OS compared to SCC. As shown in Table 6, non-SCC patients had not cured when they had recurrence or progressed disease. Therefore, a longer follow-up period may result in a difference in OS. To overcome this problem, it is essential to increase the number of non-SCC patients and extend the follow-up period sufficiently. However, the results of this study will contribute to revealing the prognosis of locally advanced UCC.

In conclusion, this study showed significantly worse prognosis in patients with non-SCC histology than in those with SCC histology of locally advanced UCC treated with definitive radiotherapy with or without concurrent chemotherapy, and this accords with the results of previous studies. To improve the survival rate of patients with locally advanced cervical cancer by focusing on the differences in radiosensitivity according to histological type, an integrated analysis combing omics analysis and clinical studies is needed.

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Conflict of Interest

The authors declare no conflict of interest.

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