

Original Article



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Predicting prognosis according to the updated WHO classification in patients with endocervical adenocarcinoma treated with surgery and radiotherapy

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ABSTRACT

Objective: The recently updated World Health Organization classification divides endocervical adenocarcinomas (ADCs) into human papillomavirus (HPV)-associated (HPVA) and HPV-independent (HPVI) ADCs. This study aimed to investigate the differences in the clinical features and treatment outcomes between patients with HPVA and HPVI.

Methods: We retrospectively reviewed the electronic medical records and pathology slides of 123 patients with endocervical ADC who underwent radical hysterectomy and adjuvant radiation therapy. Tumor characteristics, patterns of failure, and survival outcomes were compared between HPVA and HPVI ADCs.

Results: Eighty-one (65.9%) and 42 (34.1%) patients were diagnosed with HPVA and HPVI ADCs, respectively. HPVI ADC showed more frequent positive vaginal resection margin (VRM) and peritoneal seeding than HPVA ADC. After a median follow-up of 58.1 months, local recurrence and distant metastasis were more frequently observed in HPVI ADC than in HPVA ADC. Both local recurrence-free survival (77.3% vs. 91.8%) and distant metastasis-free survival (50.1% vs. 73.7%) rates of HPVI ADC were lower than those of HPVA ADC. Disease-free survival was not significantly different between HPVI and HPVA ADCs.

Conclusion: We demonstrated that HPVI ADC exhibited higher rates of VRM involvement and peritoneal seeding than those of HPVA ADC, resulting in higher rates of local recurrence and distant metastasis. Further studies with larger populations are warranted to explore optimal treatment strategies based on the histological subtypes of endocervical ADC.

Keywords: Cervical Cancer; Adenocarcinoma; Human Papillomavirus; Radiotherapy

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Conflict of Interest

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

Author Contributions

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INTRODUCTION

Cervical cancer is the fourth most common cancer among women, with an estimated 604,000 new cases worldwide [1]. The most common histological subtype of cervical cancer is squamous cell carcinoma (SCC). Endocervical adenocarcinoma (ADC) is the second most common subtype, accounting for 10%–25% of all cervical cancer cases [2,3]. The proportion of endocervical ADC is increasing, particularly in developed countries, while the incidence of cervical SCC has decreased [4,5]. Compared with SCC, endocervical ADC has been reported to be radioresistant and exhibits distant metastasis more frequently, resulting in worse survival [6-8]. However, due to the rarity and lack of prospective studies focusing on the optimal treatment strategies for endocervical ADC, the current guidelines do not suggest approaches for ADC different from those for SCC of the uterine cervix.

Endocervical ADC comprises heterogeneous histological subtypes. The most frequent subtype is usual-type ADC, which is human papillomavirus (HPV)-related, and the second most common subtype is gastric-type ADC, which is not associated with high-risk HPV infection. Given the recognition that HPV-unrelated ADC displays aggressive biological behavior, a new classification incorporating etiology, which is assumed to be more clinically relevant, has emerged [9]. The International Endocervical Adenocarcinoma Criteria and Classification (IECC) classifies endocervical ADCs into HPV-associated (HPVA) and non-HPVA ADCs [3,10-12]. This classification is based on morphological characteristics (identifiable apical mitotic figures and apoptotic bodies which appears as a round oval mass of intensely eosinophilic cytoplasm) on hematoxylin-eosin stained slides and additional HPV test is not mandatory. The recently updated World Health Organization (WHO) classification of female genital tumors adopted the concept of IECC and also recommended dividing endocervical ADCs into HPVA and HPV-independent (HPVI) ADCs [13,14]. However, there are limited data regarding the clinical features and optimal treatment approaches based on the updated WHO classification.

This study aimed to investigate the clinical features and treatment outcomes of patients with endocervical ADC and compare the differences between HPVA and HPVI ADCs.

MATERIALS AND METHODS

We retrospectively reviewed the electronic medical records of 123 patients who underwent surgery and postoperative adjuvant radiation therapy (RT) for endocervical ADC from 2001 to 2018 in a single institution. Clinical and pathological staging was performed based on the 2018 International Federation of Gynecology and Obstetrics (FIGO) staging system using physical examination, abdominopelvic and chest computed tomography, magnetic resonance imaging (MRI), or positron emission tomography-computed tomography (PET-CT). MRI was done in all patients and PET-CT was done in 71 patients (57.3%).

All patients underwent radical hysterectomy and pelvic lymph node (LN) dissection followed by adjuvant RT with or without concurrent chemotherapy. Of all patients, a majority of patients (110/124, 88.7%) received type III hysterectomy, 9/124 (7.3%) did type I hysterectomy, and 5/124 (4.0%) did type II radical hysterectomy. And the length of vagina was recommended to be resected at least 1-2 cm from primary mass. Forty-two patients underwent para-aortic LN sampling or dissection, which was performed based on the

surgeon's preference. Adjuvant external beam RT was recommended for the patients who met more than one of the following risk factors: tumor size ≥ 4 cm, positive lympho-vascular invasion, and invasion depth of more than half of the cervical stroma. For the patients with more than one of the following criteria: LN metastasis, parametrial invasion, and positive resection margin, adjuvant RT with concurrent chemotherapy was recommended. Adjuvant external beam RT to the whole pelvis was administered to all patients with a total dose of 45–50.4 Gy in 25–28 fractions five times per week. Extended-field RT with the upper margin up to T12–L1 was performed in 10 patients with para-aortic LN involvement. Additional intracavitary brachytherapy was administered to five patients with a close (≤ 5 mm) or positive vaginal resection margin (VRM) with a total dose of 10–18 Gy in 2–6 fractions. The concurrent chemotherapy regimen comprised weekly cisplatin for six cycles or 5-fluorouracil and cisplatin every 3 weeks for 2–3 cycles.

A single experienced pathologist specialized in gynecological oncology (H.-S.K.) reviewed all available hematoxylin and eosin-stained slides and determined the histological subtypes based on the IECC criteria [10] and updated WHO classification [14]. Endocervical ADCs with easily identified apical mitotic figures and apoptotic bodies were considered to be HPVA ADC. HPVA ADCs were further subcategorized based on the cytoplasmic features: 1) usual-type ($\leq 50\%$ of the tumor cells with appreciable intracytoplasmic mucin); 2) mucinous-type, not otherwise specified (NOS; $> 50\%$ of the tumor cells with intracytoplasmic mucin in a background of usual-type endocervical ADC); 3) mucinous-type, intestinal ($\geq 50\%$ of the tumor cells with goblet morphology in a background of usual-type endocervical ADC); and 4) mucinous-type, invasive stratified mucin-producing (ISM; invasive nests of stratified columnar cells with peripheral palisading, numerous intraepithelial neutrophils, and variable amounts of intracytoplasmic mucin). Meanwhile, if the tumor demonstrated no readily identifiable apical mitotic activity and apoptotic bodies or showed focal/equivocal HPVA ADC features only appreciable at high-power ($200\times$) magnification, it was considered as HPVI ADC. HPVI ADCs were subclassified based on the established morphological criteria as follows: 1) gastric-type (abundant clear, foamy, or pale eosinophilic cytoplasm; distinct cytoplasmic borders; low nuclear-cytoplasmic ratio; and prominent desmoplastic stromal reaction); 2) clear cell-type (solid, papillary, and tubulocystic architecture and polygonal tumor cells with highly atypical, but uniform nuclei); 3) mesonephric-type (intraluminal eosinophilic colloid-like material resembling mesonephric remnants and various architectural patterns, including tubular, ductal, papillary, solid, spindle, retiform, sex cord-like, etc.); 4) serous-type (papillary and micropapillary architecture and diffusely distributed tumor cells showing highly atypical nuclei and relative lack of intercellular adhesion); and 5) NOS (unclassifiable).

Patient and tumor characteristics were compared between HPVI and HPVA ADCs using Fisher's exact test for categorical variables and the Mann-Whitney U-test for continuous variables. Local recurrence was defined as a recurrent tumor at the vaginal stump. Regional recurrence was defined as recurrence within the regional LNs, including common iliac and para-aortic LNs. Distant failure was defined as recurrent disease outside the pelvis or regional LNs. Local recurrence-free survival (LRFS), regional recurrence-free survival (RRFS), and distant metastasis-free survival (DMFS) were defined as the interval from the date of surgery to the date of local recurrence, regional recurrence, and distant failure or last follow-up, respectively. Disease-free survival (DFS) and overall survival (OS) were defined as the interval from the date of surgery to the date of recurrence or last follow-up and from the date of surgery to the date of death or last follow-up, respectively. Survival rates were calculated

using the Kaplan-Meier method and compared using the log-rank test for univariate analysis. Multivariate analysis was performed using hazard ratios (HRs) and 95% confidence intervals (CIs), derived from a Cox proportional hazards model. A $p < 0.05$ was considered statistically significant. All analyses were conducted using the Statistical Package for the Social Sciences version 27 (SPSS Inc., IBM, Armonk, NY, USA).

1. Ethics approval and consent to participate

This study was approved by the Institutional Review Board of the Samsung Medical Center (approval number: 2020-10-052-001).

RESULTS

1. Patient and tumor characteristics

Table 1 summarizes the patient and tumor characteristics and their differences between HPV-A and HPV-I ADCs. The median age of the patients was 48 years (range, 16–67 years). The median tumor size was 4.0 cm (range, 0.7–11.0 cm). Eighty-one (65.9%) and 42 (34.1%) tumors were classified as HPV-A and HPV-I ADCs, respectively (**Fig. 1**). In HPV-A ADC, the most common subtype was the usual type (60/81, 74.0%), followed by the mucinous type-ISM

Table 1. Patient and tumor characteristics

Characteristics	Total	HPV-associated adenocarcinoma	HPV-independent adenocarcinoma	p-value
No. of patients	123	81	42	
Median age (range) (yr)	48 (16–67)	48 (28–76)	48 (16–67)	0.731
Median tumor size (range) (cm)	4.0 (0.7–11.0)	4.1 (0.8–11.0)	3.85 (0.7–10.0)	0.513
Clinical FIGO stage (2018)				0.195
I	69 (56.1)	41 (50.6)	28 (66.7)	
II	12 (9.8)	8 (9.9)	4 (9.5)	
III	42 (34.1)	32 (39.5)	10 (23.8)	
Pathological FIGO stage (2018)				0.051
IB	39 (31.7)	30 (37.0)	9 (21.4)	
IIA	22 (17.9)	15 (18.5)	7 (16.7)	
IIB	13 (10.6)	4 (4.9)	9 (21.4)	
IIIC1	39 (31.7)	25 (30.9)	14 (33.3)	
IIIC2	10 (8.1)	7 (8.6)	3 (7.1)	
Depth of invasion				0.454
≤50%	22 (17.9)	16 (19.8)	6 (14.3)	
>50%	91 (74.0)	60 (74.1)	31 (73.8)	
Unknown	10 (8.1)	-	-	
Parametrial invasion				0.002*
No	91 (74.0)	67 (82.7)	24 (57.1)	
Yes	32 (26.0)	14 (17.3)	18 (42.9)	
Vaginal resection margin				0.005*
Negative	112 (91.1)	78 (96.3)	34 (81.0)	
Positive	11 (8.9)	3 (3.7)	8 (19.0)	
Lymphovascular space invasion				0.233
No	56 (45.5)	40 (49.4)	16 (38.1)	
Yes	67 (54.5)	41 (50.6)	26 (61.9)	
Lymph node involvement				0.396
No	68 (55.3)	40 (49.4)	16 (38.1)	
Yes	55 (44.7)	41 (50.6)	26 (61.9)	
Adjuvant RT				0.188
RT alone	51 (41.5)	37 (45.7)	14 (33.3)	
CCRT	72 (58.5)	44 (54.3)	28 (66.7)	

Values are presented as number (%) unless otherwise indicated.

CCRT, radiation therapy with concurrent chemotherapy; HPV, human papillomavirus; RT, radiation therapy.

*Statistically significant.

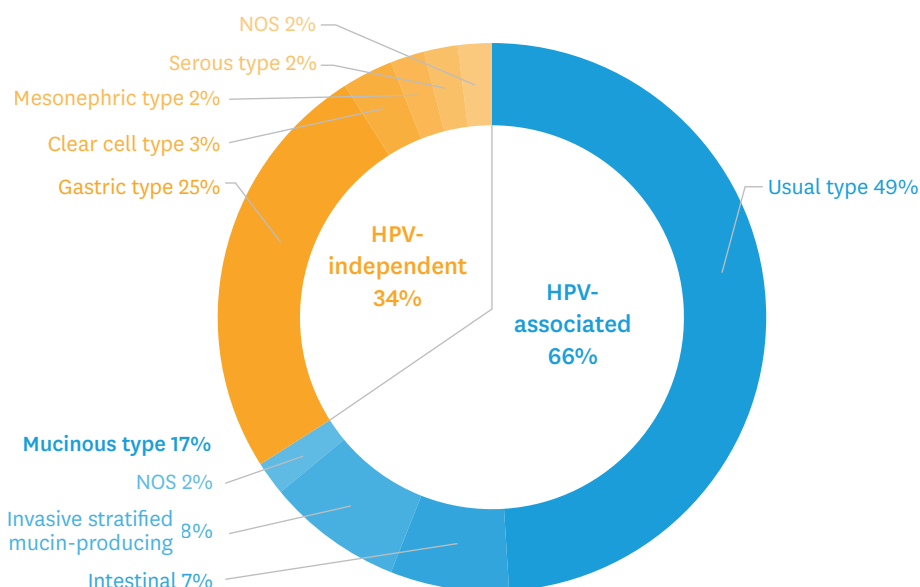


Fig. 1. Percentage of 123 cases of endocervical adenocarcinoma classified by the updated 2020 World Health Organization classification.
HPV, human papillomavirus; NOS, not otherwise specified.

(10/81, 12.3%), mucinous type-intestinal (8/81, 9.9%), and mucinous type-NOS (3/81, 3.7%). In HPVI ADC, the gastric type was the most common (30/42, 71.4%). We also identified four (9.5%), three (7.1%), three (7.1%), and two (4.8%) cases of the clear cell type, mesonephric type, serous type, and NOS, respectively.

Sixty-one (49.6%) patients were diagnosed with stage IB–IIA disease, 13 (10.6%) had stage IIB disease, and 49 (39.8%) had stage III disease (IIIC1, 31.7%; IIIC2, 8.1%). There was a marginal difference in the stage distribution ($p=0.051$) between HPVA and HPVI ADCs. Parametrial invasion (42.9% vs. 17.3%, $p=0.002$) and VRM involvement (19.0% vs. 3.7%, $p=0.005$) were more frequent in patients with HPVI ADC. Median age, tumor size, lymphovascular space invasion, and LN involvement did not differ significantly between the groups. Adjuvant RT with concurrent chemotherapy (concurrent chemoradiation therapy, CCRT) was administered to 44 (54.3%) and 28 (66.7%) patients with HPVA and HPVI ADCs, respectively.

2. Patterns of failure

After a median follow-up of 58.1 months (range, 3.9–235.5 months), 47 (38.2%) patients experienced disease recurrence, and 35 (28.5%) patients died. As the first recurrence, distant failure was the most common failure pattern (42/123, 34.1%), followed by regional (22/123, 17.9%) and local (15/123, 12.2%; **Table 2**) failures. Compared with the HPVA group, the HPVI group showed higher rates of local recurrence (19.0% vs. 8.6%, $p=0.094$) and distant

Table 2. Patterns of failure

Patterns	Total	HPV-associated adenocarcinoma	HPV-independent adenocarcinoma	p-value
Local failure	15 (12.2)	7 (8.6)	8 (19.0)	0.094
Regional failure	22 (17.9)	14 (17.3)	8 (19.0)	0.809
Distant failure	42 (34.1)	22 (27.2)	20 (47.6)	0.023*
Total	47	27	20	

Values are presented as number (%).

HPV, human papillomavirus.

*Statistically significant.

metastasis (47.6% vs. 27.2%, $p=0.023$). Regional recurrence did not differ between the groups. The most common site of distant metastasis was the lungs (14/42, 33.3%), followed by peritoneal seeding (11/42, 26.2%; **Table S1**). Peritoneal seeding was more frequently observed in HPV-I ADCs (16.7% vs. 3.7%, $p=0.013$).

3. Survival outcomes

In all patients, the 5-year DFS and OS rates were 58.2% and 71.3%, respectively. Kaplan-Meier curves for DFS, LRFS, RRFS, and DMFS are illustrated in **Fig. 2**. DFS of HPV-I ADC was inferior to that of HPV-A ADC; however, the difference was not statistically significant (48.0% vs. 63.6%, $p=0.168$). HPV-I ADC (77.3%) showed a lower LRFS than HPV-A ADC (91.8%), and the difference was marginally significant ($p=0.098$). DMFS was significantly lower in HPV-I ADC (50.1%) than in HPV-A ADC (73.7%; $p=0.029$). Differences among the subclassified histological types were not statistically significant in the HPV-A and HPV-I groups (**Fig. S1**).

4. Prognostic factors

In all patients, univariate and multivariate analyses were performed to identify significant prognostic factors for DFS, LRFS, and DMFS (**Tables 3 and 4**). Histology, the pathological

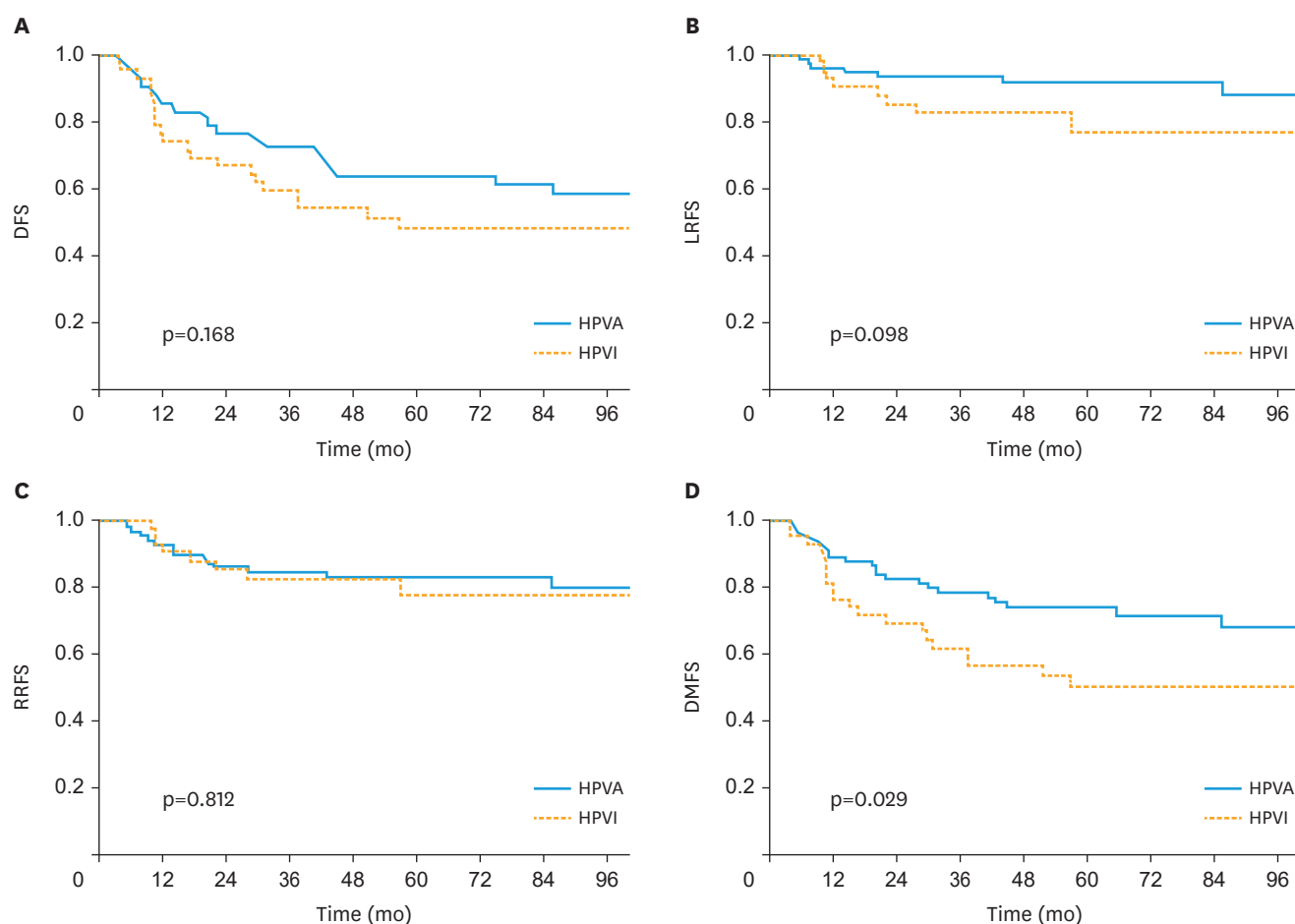


Fig. 2. Kaplan-Meier plots for (A) disease-free survival, (B) local recurrence-free survival, (C) regional recurrence-free survival, and (D) distant metastasis-free survival of patients with HPV-associated or HPV-independent endocervical adenocarcinomas. DFS, disease-free survival; DMFS, distant metastasis-free survival; HPVA, HPV-associated; HPV-I, HPV-independent; LRFS, local recurrence-free survival; RRFS, regional recurrence-free survival; HPV, human papillomavirus.

New WHO classification of cervical adenocarcinoma

Table 3. Univariate analysis for disease-free survival, local-recurrence free survival, and distant-metastasis free survival

Characteristics	5-yr disease-free survival		5-yr local recurrence-free survival		5-yr distant metastasis-free survival	
	Survival rate	p-value	Survival rate	p-value	Survival rate	p-value
Histology						
HPV-associated	63.6%	0.168	91.8%	0.098	73.7%	0.029*
HPV-independent	48.0%		77.3%		50.1%	
Clinical FIGO stage (2018)						
I	67.0%	0.016	86.4%	0.802	70.9%	0.127
II	71.4%		85.7%		71.4%	
III	39.6%		88.7%		54.3%	
Pathological FIGO stage (2018)						
IB	83.9%	<0.001*	97.4%	0.034*	86.3%	<0.001*
IIA	81.0%		90.5%		85.0%	
IIB	20.8%		91.7%		49.9%	
IIIC1	42.2%		78.8%		48.9%	
IIIC2	15.0%		36.0%		20.0%	
Depth of invasion						
≤50%	76.4%	0.248	90.4%	0.796	81.6%	0.266
>50%	53.8%		84.7%		62.3%	
Parametrial invasion						
No	70.2%	<0.001*	89.6%	0.307	75.7%	<0.001*
Yes	22.4%		73.4%		33.5%	
Vaginal resection margin						
Negative	62.6%	0.001*	91.2%	<0.001*	70.9%	<0.001*
Positive	18.2%		37.3%		18.2%	
Lymph node involvement						
No	76.6%	<0.001*	96.9%	0.002*	81.2%	<0.001*
Yes	36.3%		72.7%		46.0%	

HPV, human papillomavirus.

*Statistically significant.

Table 4. Multivariate analysis for disease-free survival, local recurrence free survival, distant metastasis free survival

Characteristics	Disease-free survival		Local recurrence-free survival		Distant metastasis-free survival	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Total						
HPVI (vs. HPVA)	1.030 (0.550–1.927)	0.927	1.812 (0.609–5.392)	0.285	1.425 (0.728–2.790)	0.302
Stage IIB (vs. I-IIA)	3.701 (1.158–11.822)	0.027*	0.275 (0.024–3.149)	0.299	2.812 (0.752–10.508)	0.124
Stage IIIC (vs. I-IIA)	3.650 (1.427–9.337)	0.007*	1.201 (0.285–5.066)	0.803	4.307 (1.528–12.144)	0.006*
VRM-positive (vs. negative)	1.749 (0.791–3.866)	0.167	4.506 (1.323–15.349)	0.016*	2.048 (0.900–4.661)	0.088
Adjuvant CCRT (vs. RT alone)	1.246 (0.479–3.237)	0.652	3.831 (0.629–23.329)	0.145	1.056 (0.374–2.984)	0.917
HPVA only						
Stage IIB (vs. I-IIA)	17.230 (2.440–121.683)	0.004*	NA	NA	14.906 (1.041–213.451)	0.047*
Stage IIIC (vs. I-IIA)	9.829 (1.970–49.029)	0.005*	8.822 (0.416–187.221)	0.162	23.815 (3.821–148.407)	0.001*
VRM-positive (vs. negative)	1.528 (0.348–6.698)	0.574	NA	NA	2.065 (0.459–9.295)	0.345
Adjuvant CCRT (vs. RT alone)	0.425 (0.087–2.087)	0.292	0.460 (0.022–9.615)	0.616	0.190 (0.034–1.056)	0.058
HPVI only						
Stage IIB (vs. I-IIA)	1.430 (0.315–6.502)	0.643	0.074 (0.005–1.178)	0.065	1.412 (0.308–6.474)	0.657
Stage IIIC (vs. I-IIA)	1.805 (0.468–6.969)	0.392	0.295 (0.039–2.224)	0.236	1.954 (0.515–7.414)	0.325
VRM-positive (vs. negative)	1.852 (0.693–4.949)	0.219	11.290 (1.884–67.656)	0.008*	1.871 (0.665–4.770)	0.251
Adjuvant CCRT (vs. RT alone)	2.761 (0.629–12.118)	0.178	NA	NA	2.463 (0.560–10.830)	0.233

CCRT, radiation therapy with concurrent chemotherapy; CI, confidence interval; HPVA, human papillomavirus-associated adenocarcinomas; HPVI, human papillomavirus-independent adenocarcinomas; HR, hazard ratio; VRM, vaginal resection margin; RT, radiation therapy.

*Statistically significant.

FIGO stage, depth of invasion, parametrial invasion, VRM involvement, and LN involvement were evaluated by univariate analysis. The FIGO stage, VRM involvement, and adjuvant treatment were included in the multivariate analysis, while parametrial invasion and LN involvement were excluded due to multicollinearity with the FIGO stage. In the univariate analysis, the FIGO stage ($p=0.034$), positive VRM ($p<0.001$), and LN involvement ($p=0.002$) were found to be significant predictors of LRFS. Histology ($p=0.029$), the FIGO stage

($p < 0.001$), parametrial invasion ($p < 0.001$), positive VRM ($p < 0.001$), and LN involvement ($p < 0.001$) significantly predicted DMFS. In the multivariate analysis, the only significant factors for LRFS and DMFS were positive VRM (HR=4.506, 95% CI=1.323–15.349, $p=0.016$) and the FIGO stage IIIC (vs. stage I–IIA; HR=4.307, 95% CI=1.528–12.144, $p=0.006$).

Survival analyses were also performed for patients included in the HPVA and HPVI groups. Patients with FIGO stage IIB HPVA ADC showed significantly lower DFS than those with I–IIA tumors (HR=17.230, 95% CI=2.440–121.683, $p=0.004$). We also observed a significant difference in the DFS between FIGO stage IIIC and I–IIA HPVA ADCs (HR=9.829, 95% CI=1.970–49.029, $p=0.005$). In contrast, the FIGO stage was not significantly associated with DFS in patients with HPVI ADC. Instead, positive VRM was the only independent prognostic factor for LRFS in patients with HPVI ADC (HR=11.290, 95% CI=1.884–67.656, $p=0.008$).

DISCUSSION

This study showed that the HPVI ADC tended to present worse prognosis compared to HPVA ADC supporting the validity of new WHO classification of endocervical ADC. This finding is noteworthy because it suggests that endocervical ADC consisted of two groups (HPVI and HPVA) with largely distinct prognosis. Previous studies have reached conflicting conclusions about the outcomes of patients with ADC and SCC of the uterine cervix [15]. While many studies documented worse survival outcomes of ADC compared with SCC [2,16,17], several other studies failed to demonstrate any difference in prognosis between patients with ADC and SCC, particularly in early-stage diseases [18,19]. One possible reason for the discrepancies might be that endocervical ADC is not a homogeneous disease but a heterogeneous group of tumors with diverse morphologies and prognoses [20–22].

Recently, several literatures reported on the prognosis difference between HPVI and HPVA ADC. Jung et al. [3] reported that the HPVI ADC was associated with bulky tumor, deep stromal invasion, and consequently worse DFS compared to usual type ADC. A multi-institutional study from Japan also have reported gastric type ADC was more associated with larger tumors, deep stromal invasion, lymphovascular invasion, and ovarian metastasis compared usual type ADC [21]. In line with previous studies, our data also showed the HPVI ADC had lower DFS by 15% than HPVA ADC at 5 years, although the difference was not statistically significant. We attempted to reveal the difference between the two subgroups focusing on clinical features and patterns of failure in order to obtain information about optimal treatment to improve the oncologic outcomes of endocervical ADC. The first point of this study is that HPVI ADC showed higher rates of VRM-positive in pathologic report. Another interesting finding is that FIGO stage was not prognostic for HPVI ADC. High rates of peritoneal seeding in HPVI ADC was also a notable finding.

The patients with HPVI ADC also had stage IIB disease more frequently, and notably, 19.0% (8/42) of them showed positive VRM following radical hysterectomy. Consistent with these results, Jung et al. [3] reported more frequent VRM involvement of gastric-type HPVI ADC compared with usual-type HPVA ADC. It can be assumed that the reason of more frequent close/positive margins in HPVI ADC is due to its infiltrative patterns of spread. Furthermore, ill-defined tumor margin on MRI of HPVI ADC might have made it difficult to estimate a sufficient resection margin [23]. Given that VRM involvement was a strong prognostic factor for LRFS with high HRs of 4.506 for all ADCs and 11.290 for HPVI ADC even after

adjuvant RT, more attention should be paid to achieve sufficient VRM, particularly in radical hysterectomy for HPVI ADC. Furthermore, the benefit of intensified RT should be investigated to improve local control in cases of margin-positive endocervical ADC. In this study, among the 11 endocervical ADC patients with positive VRM, five patients underwent additional brachytherapy on the vaginal stump, and the six other patients did not. In both groups, two patients experienced local recurrence, which could not imply the effect of brachytherapy. Large sample sizes or long follow-up periods are necessary to clarify the therapeutic implications of vaginal brachytherapy for margin-positive endocervical ADC.

Interestingly, FIGO stage was not prognostic for HPVI ADC. Although it is cautious to generalize the results of this study due to the small number of patients, it might be because the current FIGO staging system had been established based on mainly SCC. The prognostic significance of the current FIGO staging system in HPVI ADC needs to be evaluated in further studies. In HPVI ADC, there was no isolated local-regional recurrence, while all recurrent diseases developed distant failures within 6 months from the first recurrence. This result is similar to that of previous studies reporting higher rates of distant metastasis in HPVI ADC [15,17,21]. Effective systemic therapy seems to be a crucial component in improving the treatment outcomes of HPVI ADC. For early-stage HPVI ADC with adverse features such as larger tumors, deep stromal invasion, and/or lymphovascular invasion, the addition of CCRT could be considered, and for advanced disease with LN involvement, additional chemotherapy after CCRT should be considered. A subgroup analysis of the Southwest Oncology Group 8797 trial [24] showed that patients with endocervical ADC had a worse prognosis than those with SCC in the adjuvant RT alone group, while the survival difference disappeared in the CCRT group. Regarding consolidation chemotherapy, although preliminary results of OUTBACK trial (NCT00980954) recently reported that adjuvant chemotherapy after CCRT did not improve survival [25], it deserves to be further investigated, especially in HPVI ADC.

This study has several limitations, including its retrospective nature and potential bias. First, this study included a relatively small number of cases, leading to low statistical power. Moreover, with a limited number of cohorts, the clinical features of rare histological subtypes could not be identified. Although survival curves for histological subtypes of HPVI ADC showed statistical differences among subtypes, the number of each subtype was too small to interpret the results. Lastly, this study included a specific patient population of those with early-stage with intermediate/high risk features requiring adjuvant RT and the findings of this study have limitations in generalizing them. Further studies with larger populations might provide more information about risk stratification strategies for patients with HPVI and HPVA ADCs.

We demonstrated that HPVI ADC had higher rates of VRM involvement and peritoneal seeding than HPVA ADC. High rates of both local and distant recurrences in patients with HPVI ADC suggest that more intensified adjuvant treatment other than the standard treatment for SCC might be necessary for this group. Further large-scale cohort studies are warranted to provide additional clinical implications.

SUPPLEMENTARY MATERIALS

Table S1

Site of distant metastasis

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Fig. S1

Kaplan-Meier plots for disease-free survival according to the histological subtypes of (A) HPV-associated and (B) HPV-independent endocervical adenocarcinomas.

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