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CLINICAL INVESTIGATION

The Updated World Health Organization Classification Better Predicts Survival in Patients With Endocervical Adenocarcinoma (KROG 20-07)

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Purpose: The 2020 World Health Organization classification divided endocervical adenocarcinoma (ADC) into human papillomavirus–associated (HPVA) and human papillomavirus–independent (HPVI) ADCs. This multi-institutional study aimed to investigate the clinical features and prognosis of patients with endocervical ADC based on the updated World Health Organization classification.

Methods and Materials: We retrospectively reviewed the 365 patients with endocervical ADC who underwent radical hysterectomy from 7 institutions. Tumor characteristics, patterns of failure, and survival outcomes were compared between HPVA and HPVI ADCs.

Results: Two hundred seventy-five (75.3%) and 90 (24.7%) patients had HPVA and HPVI ADC diagnoses, respectively. In all cases, the 5-year disease-free survival (DFS) and overall survival (OS) rates were 58.2% and 71.3%, respectively. HPVI ADC showed higher rates of local recurrence (25.6% vs 10.9%) and distant metastasis (33.3% vs 17.5%) than HPVA ADC. Multivariate survival analysis revealed that HPVI ADC showed significantly worse DFS (hazard ratio [HR], 1.919; 95% confidence interval [CI], 1.324-2.781; $P < .001$), distant metastasis-free survival (HR, 2.100; 95% CI, 1.397-3.156; $P < .001$), and OS (HR, 2.481; 95% CI, 1.586-3.881; $P < .001$) than HPVA ADC. Patients with gastric- and serous-type HPVI ADC had significantly worse

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OS than those with other HPVI ADCs ($P = .020$). Similarly, invasive stratified mucin-producing−type HPVA ADC showed significantly worse OS than other HPVA ADCs ($P < .001$).

Conclusions: We demonstrated that HPVI ADC exhibited inferior DFS and OS and higher rates of local and distant recurrence compared with HPVA ADC. Gastric- and serous-type HPVI ADCs and invasive stratified mucin-producing−type HPVA ADC showed worse OS than other types of HPVI and HPVA ADCs, respectively. Our observation of significant differences in prognoses according to the histologic types needs to be validated in larger cohorts of patients with endocervical ADC.

Introduction

Cervical cancer is the fourth most common cancer among women worldwide and still the most common cause of death in developing countries.[1] Endocervical adenocarcinoma (ADC) is the second most common histologic type in cervical cancer, and the prognosis is known to be poor compared to squamous cell carcinoma (SQC).[2-4] However, it is not established whether the treatment approach for endocervical ADC should differ from that for SQC. As the relative proportion of endocervical ADC increases recently, the optimal treatment strategies for endocervical ADC are getting a lot of attention. According to the 2014 World Health Organization (WHO) classification, endocervical ADC was classified into several morphological types; however, there are few studies regarding the clinical implication of this classification.

Recently, the WHO classification of cervical cancer was revised to report the association with human papillomavirus (HPV) prior to morphological types.[5] The revision was based on the studies from the International Endocervical Adenocarcinoma Criteria and Classification (IECC), which attempted to categorize endocervical ADC into HPV-associated (HPVA) and HPV-independent (HPVI) groups based on morphology alone. Since apical mitotic figures and apoptotic bodies readily identifiable at scanning magnification are characteristic of HPVA ADC, additional molecular test and immunostaining are not mandatory. This histology-based classification was highly concordant with the results of HPV RNA in situ hybridization and p16 immunostaining in multinational studies.[6,7]

However, the clinical implication of the updated WHO classification has not been sufficiently investigated yet. Because prospective large-scale studies are practically limited due to its rarity, we performed a multi-institutional retrospective study. This study aimed to investigate the clinical features and prognosis of patients with endocervical ADC based on the updated WHO classification.

Methods and Materials

Patients

We retrospectively reviewed electronic medical records of 365 patients who were diagnosed as endocervical ADC after surgery from 2001 to 2018 in 7 institutions included in the Korean Radiation Oncology Group. Staging was based on the 2018 International Federation of Gynecology and Obstetrics staging system using physical examination, abdominopelvic and chest computed tomography, magnetic resonance imaging, or positron emission tomography −computed tomography.

Treatment

All patients underwent radical hysterectomy and pelvic lymph node (LN) dissection. Para-aortic LN dissection was done in 130 patients based on the surgeon's preference. Following surgery, adjuvant concurrent chemoradiation therapy (CCRT) was recommended for high-risk patients with 1 of the following factors: LN metastasis, parametrial invasion, and positive resection margin involvement. Adjuvant radiation therapy (RT) alone was recommended for intermediate-risk patients with >1 of the following factors: tumor size ≥4 cm, positive lymphovascular space invasion (LVSI), and invasion depth >50% of the cervical stroma. Finally, adjuvant RT alone and CCRT was administered to 102 (27.9%) and 194 (23.2%) patients, respectively. However, based on the discretion of their physicians and the preference of the patients, 7 (1.9%) and 3 (0.8%) patients received sequential chemoradiotherapy and chemotherapy (CTx) alone, respectively. Of all patients, 303 patients received adjuvant RT, and all of them received external team RT, including whole pelvis with a total dose of 45 to 50.4 Gy in 25 to 28 fractions 5 times per week. Among those who received adjuvant RT, extended-field RT was applied to 8.9% of the patients (27/303). In addition to external beam RT, brachytherapy boost was applied to 71 patients with a dose of 10 to 35 Gy in 2 to 7 fractions.

Pathological review

To determine the histologic type according to the most recent WHO classification, the pathological review was conducted by a group of board-certified pathologists specialized in gynecological oncology. Seven gynecological pathologists were recruited from 7 institutions in Republic of Korea to participate in this study. Reviewers were blinded to all clinicopathological characteristics, HPV status, and patient identity of each case. Written instructions were provided to each reviewer summarizing the diagnostic criteria of WHO classification and IECC in tabular and graphic formats.[8,9] Slide

review and diagnosis assignment were conducted independently. During the study period, regular consensus meeting and online training for quality assurance purposes was held using at least a proportion of specimens. Even though the review process was based on evaluation of routine hematoxylin and eosin–stained slides only, for very a few challenging cases showing unusual or ambiguous histology, the immunohistochemical and genetic profiles were provided, and the reviewers rendered a final diagnosis. Representative photomicrographs of HPVA and HPVI ADCs are shown in Fig. 1. Tumors with apical mitotic figures and apoptotic bodies readily identifiable at scanning magnification

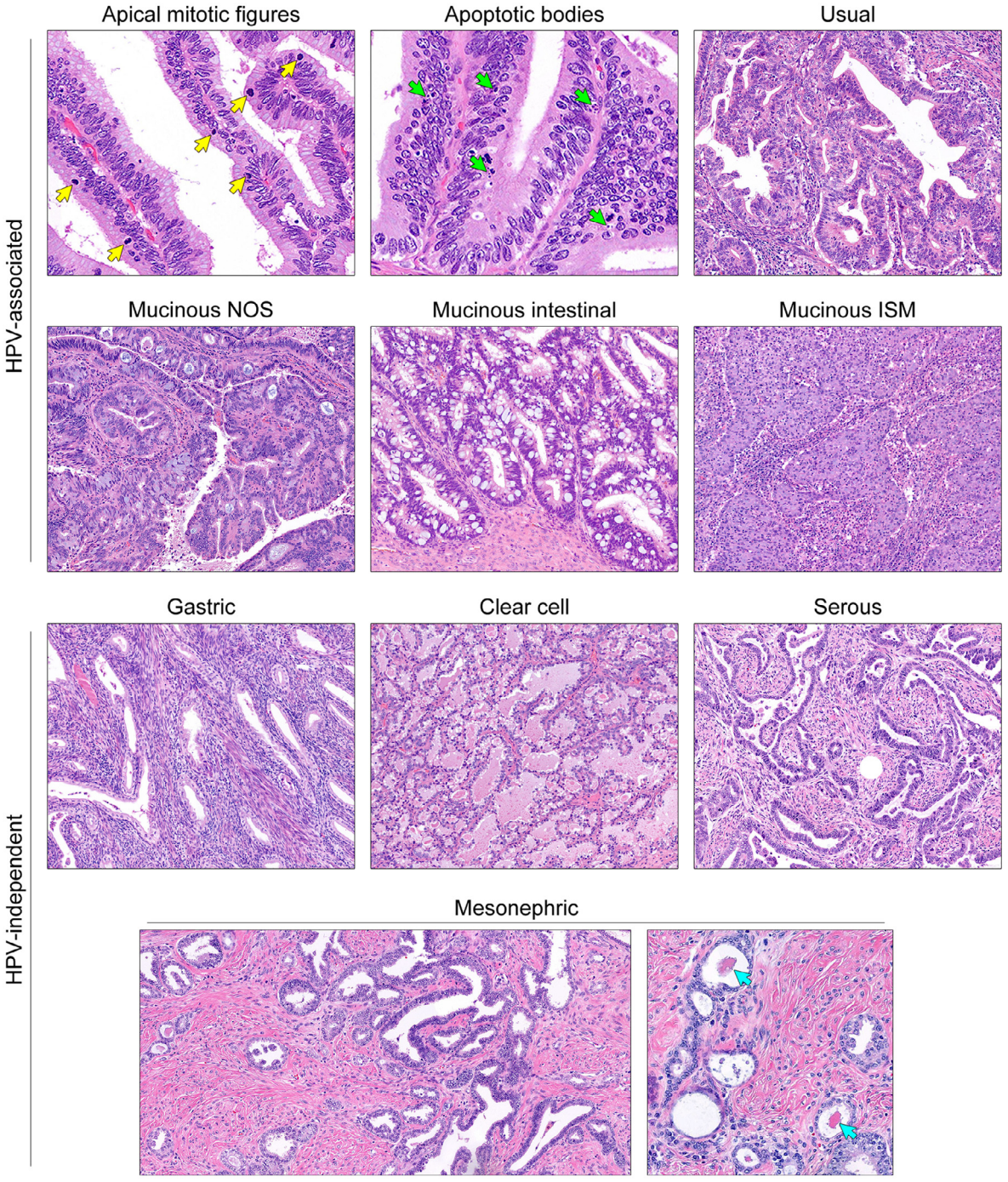

Fig. 1. Representative photomicrographs showing histologic features of HPV-associated (upper 2 panels) and HPV-independent (lower 2 panels) ADCs. HPV-associated ADCs are characterized by easily identifiable apical mitotic figures (yellow arrows) and apoptotic bodies (green arrows). Mesonephric-type HPV-independent ADC characteristically exhibits densely eosinophilic intraluminal secretions (blue arrows). *Abbreviations:* ADC = endocervical adenocarcinoma; HPV = human papillomavirus; ISM = invasive stratified mucin producing; NOS = not otherwise specified.

were considered as HPVA ADC. HPVA ADCs were further subcategorized based on the cytoplasmic features as follows: (1) usual type (≤50% of the tumor cells with appreciable intracytoplasmic mucin); (2) mucinous not otherwise specified (NOS) type (>50% of the tumor cells with intracytoplasmic mucin in the usual-type ADC background); (3) mucinous intestinal type (≥50% of the tumor cells with goblet morphology in the usual-type ADC background); (4) mucinous signet-ring cell type (>50% of the tumor cells with signet-ring morphology in the ADC background); and (5) invasive stratified mucin-producing (ISM) type (invasive nests of stratified columnar cells with peripheral nuclear 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 HPV infection−related features only appreciable at high-power magnification, it was considered as HPVI ADC. HPVI ADCs were subclassified as follows: (1) gastric type (abundant, mucin-containing cytoplasm, and prominent stromal desmoplasia); (2) clear cell type (solid, papillary, and tubulocystic architecture; polygonal cells with highly atypical nuclei); (3) mesonephric type (eosinophilic intraluminal secretions and various architectural patterns, such as tubular, ductal, papillary, and solid); (4) serous type (papillary and solid architecture showing markedly atypical tumor cells and relative lack of intercellular adhesion); and (5) NOS (unclassifiable).

Statistical analysis

Patient and tumor characteristics were compared between HPVI and HPVA ADCs using the Fisher 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. Locoregional recurrence-free survival (LRRFS) and distant metastasis-free survival (DMFS) were defined as the interval from the date of surgery to the date of local or 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 value <.05 was considered statistically significant. All analyses were conducted using the Statistical Package for the Social Sciences, version 27 (SPSS Inc, IBM, Armonk, NY).

Ethics

This study was approved by the institutional review board of the Samsung Medical Center (approval number: 2020-10-052-001).

Results

Patient and tumor characteristics

Of all patients, 275 (75.3%) and 90 (24.7%) cases were classified as HPVA and HPVI ADCs, respectively. The proportions of histologic types are described in Table 1. In HPVA ADC, the most common type was the usual type (217/275, 78.9%). In HPVI ADC, gastric type was the most common (57/90, 63.3%).

The patient and tumor characteristics and their differences between HPVA and HPVI ADCs are summarized in Table 2. The patients' median age was 47 years (range, 16-76 years). The median pathologic tumor size was 3.3 cm (range, 0.3-11.0 cm). Of all patients, 206 (56.4%) had stage IB-IIA disease, 38 (10.4%) had stage IIB disease, and 121 (33.2%) had stage III disease (IIIC1, 29.9%; IIIC2, 3.3%). In HPVA ADC, stage IB-IIA was more frequent (61.1% vs 42.2%), and stage IIB (7.6% vs 18.9%) and IIIC (31.3% vs 38.8%) were less frequent than HPVI ADC (P = .003). Median age did not differ significantly between the groups. Median tumor size was larger in HPVI ADC than in HPVA ADC (3.0 vs 3.7 cm; P = .007). Parametrial invasion (37.8% vs 18.9%; P < .001), resection margin involvement (16.6% vs 4.3%; P = .002), and LVSI (58.9% vs 44.7%; P = .020) were more frequent in patients with HPVI ADC.

Table 1 Proportions of histologic types of ADC

Histologic type		Number of cases
HPVA ADC	Usual	217 (59.5%)
	Mucinous intestinal	19 (5.2%)
	Mucinous ISM	13 (3.6%)
	Mucinous SRC	3 (0.8%)
	Mucinous NOS	23 (6.3%)
HPVI ADC	Gastric	57 (15.6%)
	Clear cell	9 (2.5%)
	Serous	6 (1.6%)
	Mesonephric	4 (1.1%)
	NOS	14 (3.8%)
Total		365 (100.0%)

Abbreviations: ADC = adenocarcinoma; HPVA = human papillomavirus−associated; HPVI = human papillomavirus−independent; ISM = invasive stratified mucin-producing; NOS = not otherwise specified; SRC = signet-ring cell.

Table 2 Patient and tumor characteristics

Characteristic		Total	HPVA ADC	HPVI ADC	*P* value
Number of cases		365	275	90	
Median age (range), y		47 (16-76)	47 (27-76)	48 (16-75)	.074
Median tumor size (range), cm		3.3 (0.3-11.0)	3.0 (0.3-11.0)	3.7 (0.7-10.0)	.007*
FIGO stage (2018)	IB-IIA	206 (56.4%)	168 (61.1%)	38 (42.2%)	.003*
	IIB	38 (10.4%)	21 (7.6%)	17 (18.9%)	
	IIIC1	109 (29.9%)	78 (28.4%)	31 (34.4%)	
	IIIC2	12 (3.3%)	8 (2.9%)	4 (4.4%)	
Invasion depth	≤50%	101 (27.7%)	85 (30.9%)	16 (17.8%)	.047*
	>50%	246 (67.4%)	178 (64.7%)	68 (75.6%)	
	Unknown	18 (4.9%)	12 (4.4%)	6 (6.7%)	
PMI	No	249 (76.4%)	223 (81.1%)	56 (62.2%)	<.001*
	Yes	86 (23.6%)	52 (18.9%)	34 (37.8%)	
RMI	No	338 (92.6%)	263 (95.6%)	75 (83.3%)	.002*
	Yes (VRM)	18 (4.9%)	8 (2.9%)	10 (11.1%)	
	Yes (PRM)	4 (1.1%)	2 (0.7%)	2 (2.2%)	
	Yes (both)	5 (1.4%)	2 (0.7%)	3 (3.3%)	
LVSI	No	189 (51.8%)	152 (55.3%)	37 (41.1%)	.020*
	Yes	176 (48.2%)	123 (44.7%)	53 (58.9%)	
Para-aortic lymph node metastasis	No	235 (64.4%)	177 (64.4%)	58 (64.4%)	.989
	Yes	130 (35.6%)	98 (35.6%)	32 (35.6%)	
Adjuvant treatment	Not done	59 (16.2%)	54 (19.6%)	5 (5.6%)	.012*
	RT alone	102 (27.9%)	78 (28.4%)	24 (26.7%)	
	CCRT	194 (53.2%)	135 (49.1%)	59 (65.6%)	
	Sequential CTx-RT	7 (1.9%)	5 (1.8%)	2 (2.2%)	
	CTx alone	3 (0.8%)	3 (1.1%)	0 (0.0%)	

Abbreviations: CCRT = radiation therapy with concurrent chemotherapy; CTx = chemotherapy; FIGO = International Federation of Gynecology and Obstetrics; HPVA = human papillomavirus–associated; HPVI = human papillomavirus–independent; LVSI = lymphovascular invasion; PMI = parametrial invasion; PRM = parametrial resection margin; RMI = resection margin involvement; RT = radiation therapy; VRM = vaginal resection margin.
* Statistically significant.

Patterns of failure

After a median follow-up of 65.6 months (range, 0.9-245.7 months), 124 patients (34.0%) experienced disease recurrence, and 79 patients (21.6%) died. As a first failure, distant failure was the most common (62.9%), followed by local (42.7%) and regional (37.1%) failure. Patterns of first failure in all, HPVA, and HPVI ADCs are depicted in Fig. E1. As a final recurrence, distant metastasis occurred in 99 patients (27.1%), and the most common site was lung (n = 30) followed by peritoneal seeding (n = 16; Table E1).

Recurrence occurred in 81 (29.5%) and 43 (47.8%) cases in HPVA and HPVI ADC, respectively. Compared with the HPVA group, the HPVI group showed higher proportion of local recurrence (53.5% vs 37.0%; P = .078) and distant metastasis (69.8% vs 59.3%; P = .249). Peritoneal seeding was more frequently observed in HPVI ADCs (12.2% vs 1.8%; P = .001).

Survival outcomes

In all patients, the 5-year DFS, LRRFS, DMFS, and OS rates were 58.2%, 79.0%, 74.4%, and 71.3%, respectively. Survival curves of HPVA and HPVI for DFS, LRRFS, DMFS, and OS are depicted in Fig. 2. Compared to HPVA ADC, DFS, LRRFS, DMFS, and OS were significantly worse in HPVI ADC (Table E2). Survival curves of the histologic types within HPVA and HPVI are shown in Fig. 3. Differences in OS among those types within the 2 groups are summarized in Table E3. In HPVA ADC, OS of mucinous ISM type (63.5% at 5-year follow-up) was lower than other types without statistical significance (P = .147) but significant compared with usual type (87.8% at 5-year follow-up; P < .001). In HPVI ADC, OS of gastric type and serous type tend to be poorer compared to other types (56.4% and 33.3% at 5-year follow-up, respectively; P = .020).

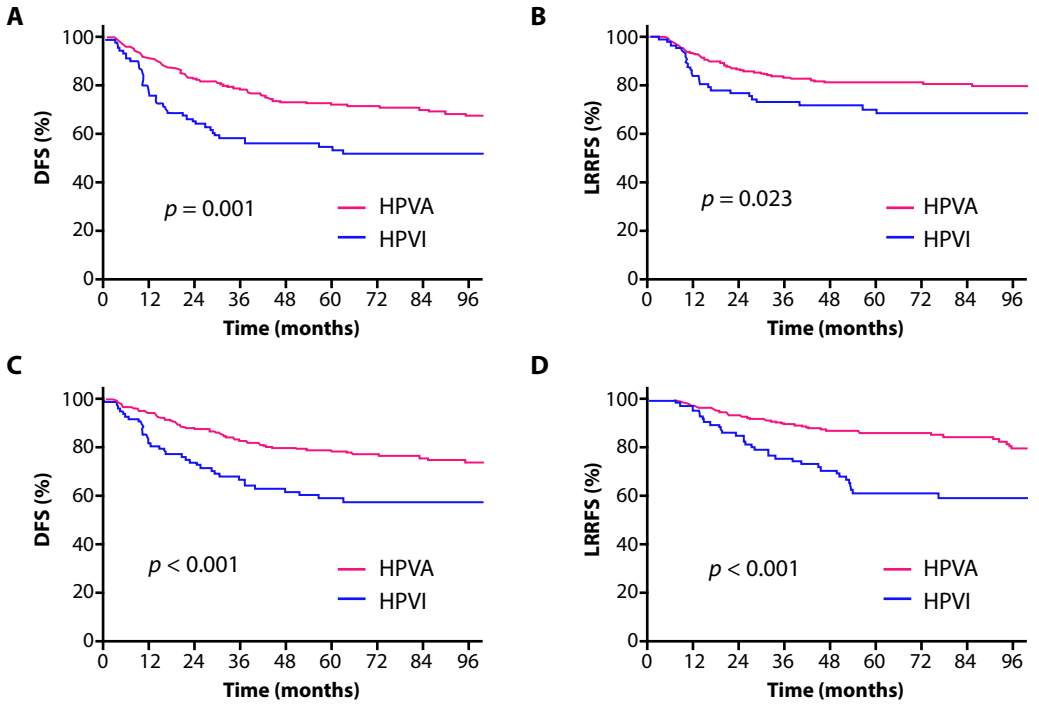

Fig. 2. Kaplan-Meier plots showing differences in (A) disease-free survival (DFS), (B) locoregional recurrence-free survival (LRRFS), (C) distant metastasis-free survival (DMFS), and (D) overall survival (OS) between human papillomavirus–associated (HPVA) and human papillomavirus–independent (HPVI) endocervical adenocarcinomas.

Prognostic factors

Table E4 shows univariate analysis for DFS, LRRFS, DMFS, and OS. Histologic subgroup (HPVI vs HPVA), International Federation of Gynecology and Obstetrics stage, depth of invasion, LVSI, parametrial invasion, resection margin involvement, and LN involvement were significant prognostic factors.

The results of multivariate analysis for survival are summarized in Table 3. HPVI ADC was an unfavorable factor for DFS ($P = .023$), DMFS ($P = .017$), and OS ($P = .005$) but not for LRRFS ($P = .132$). Other unfavorable factors were stage IIIC ($P < .001$), LVSI ($P < .001$), and deep stromal invasion (>50%; $P < .001$) for DFS; stage IIIC ($P < .001$), LVSI ($P < .001$), and deep stromal invasion ($P < .001$) for LRRFS; stage IIIC ($P < .001$), LVSI ($P < .001$), and deep stromal invasion ($P = .015$) for DMFS; and stage IIB ($P < .001$) and IIIC ($P < .001$) and LVSI ($P < .001$) for OS.

Discussion

We investigated the clinical features and prognosis of patients with endocervical ADC reclassified according to the new 2020 WHO classification. Differences in the clinical features and patient outcomes among the histologic types have not been established clearly. Several previous studies have published aggressive clinical features and poor prognosis of gastric-type ADC, which is the most common type of HPVI ADC.[10,11] Recently, IECC reported the difference in prognosis between HPVA and HPVI ADCs, which founded the basis of new classification.[6,7] In line with the previous reports, we observed that HPVI ADC had significantly worse DFS, DMFS, and OS than HPVA ADC in multivariate analysis. Distinctive survival outcomes of HPVI ADC support the validity of the updated WHO classification. Furthermore, we found distinguishing clinicopathological characteristics of HPVI ADC compared with HPVA ADC. Higher rate of local recurrence was observed in patients with HPVI ADC and high rates of distant metastasis, particularly more frequent peritoneal seeding, was also found. We also attempted to identify the difference between histologic types within each group, and we found that although the difference was not statistically significant, some types tend to have worse prognosis than other types in both HPVA and HPVI ADCs.

As is known from the previous reports, the rates of distant metastasis of our cohort were higher compared to the historical data including mostly SQC reporting the distant metastasis rate as 11% to 16% in cervical cancer,[12-14] and it was higher in HPVI ADC (33.3%) than in HPVA ADC (17.5%). The most frequent site of distant metastasis was lung in both HPVI and HPVA as is well known. However, interestingly, in HPVI ADC, peritoneal seeding was the second most common site of metastases, observed in 12.2% of

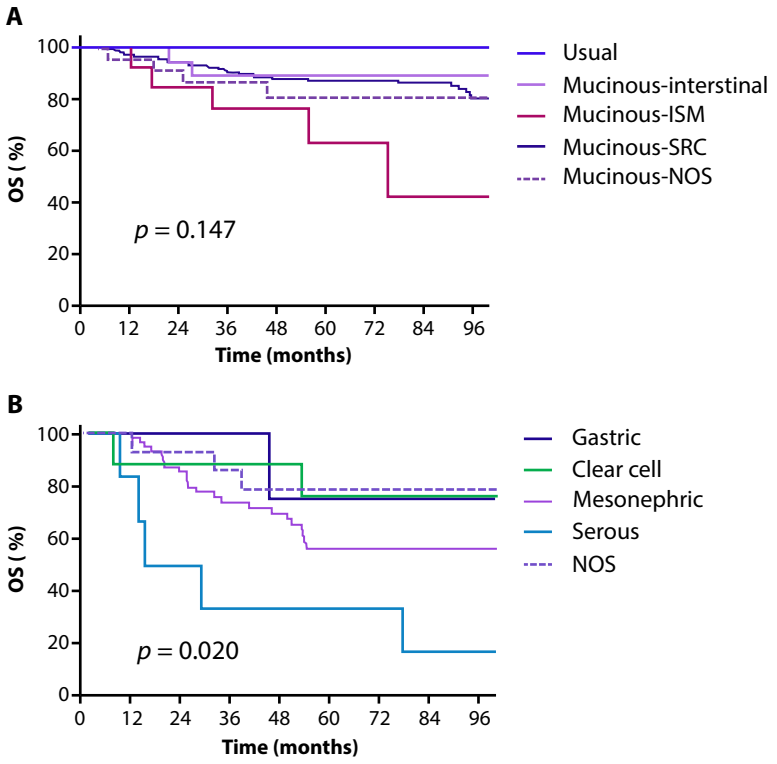

Fig. 3. Kaplan-Meier plots showing differences in OS among the histologic types within (A) HPVA and (B) HPVI endocervical adenocarcinomas. *Abbreviations:* HPVA = human papillomavirus−associated; HPVI = human papillomavirus−independent; ISM = invasive stratified mucin producing; NOS = not otherwise specified; OS = overall survival; SRC = signet-ring cell.

those cases. In fact, the abdominopelvic peritoneum is usually not a common site of metastasis in SQC patients. A population-based study reported that the rate of peritoneal seeding in cervical cancer was approximately 1%, and the risk of peritoneal involvement was 4-fold higher in ADC than in SQC.[15] These results suggest that physicians would better to pay more attention to the potential risk of peritoneal seeding in case of HPVI ADC in follow-up imaging evaluation and might consider CCRT even in pathologically low-risk patients and further systemic therapy after adjuvant RT or CCRT.

We observed that HPVI ADC was an independent factor for worse DFS, DMFS, and OS but not for LRRFS in multivariate analysis. It is understandable because the HPVI cohort had more high-risk pathological features than the HPVA cohort, which might have alleviated the significance of association between HPVI histology and LRRFS. Meanwhile, poorer DFS and OS in the HPVI ADC are the results of high rates of distant metastasis. More frequent distant metastasis in HPVI ADC suggests potential benefit of intensified CTx in this group. Although Gynecologic Oncology Group/Radiation Therapy Oncology Group 0724 (NCT00980954) trial that evaluated the survival benefit of adjuvant CTx with carboplatin and paclitaxel following concurrent chemoradiation compared to chemoradiation alone for IB-IVA cervical cancer showed negative results, the effect of additional CTx needs to be further evaluated, particularly in subgroup with HPVI ADC.[16] The molecular profiles of HPVI ADCs have been described in several previous literatures. Ren et al reported that *TP53* mutations are much more frequent in HPVI ADC and *GNAS* mutations much less frequent in comparison to HPVA ADC.[9] The frequencies of *PIK3CA* and *KRAS* mutations are slightly higher in HPVA ADC than in HPVI ADC.[17-19] In particular, approximately half of gastric-type HPVI ADCs (45%-54%) harbor pathogenic *TP53* mutations, while mutations in *ERBB2, ARID1A, BRCA2, CDKN2A*, and *STK11* have been also described in gastric-type tumors.[20] Park et al documented that the most frequently mutated gene detected in gastric-type HPVI ADC is *TP53*(52.4%), followed by *STK11, PTPRS, FGFR4, GNAS, ERBB3, KMT2D, EPCAM, SNAI1, TWIST1*, and so on.[21] In addition, gastric-type HPVI ADCs share some genetic features with gastrointestinal and pancreatobiliary adenocarcinoma, providing clues in understanding the biological and morphological basis of gastric-type HPVI ADC. Not much is known regarding the molecular underpinnings of clear cell−type HPVI ADCs.[22] Boyd et al showed that microsatellite instability was detected in all diethylstilbestrol-exposed tumors and half of non−diethylstilbestrol-exposed tumors, while no mutations were detected in *KRAS, HRAS, WT1*, or *TP53*.[23] Ueno et al suggested that the PI3K-AKT pathway is involved in the

Table 3 Multivariate survival analysis

Characteristic		DFS		LRRFS		DMFS		OS	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Histology	HPVI vs HPVA	1.559 (1.062-2.289)	.023*	1.453 (0.894-2.362)	.132	1.674 (1.095-2.558)	.017*	1.959 (1.230-3.121)	.005*
FIGO stage (2018)	IIB vs IB-IIA	1.498 (0.763-2.940)	.240	0.845 (0.326-2.193)	.729	1.499 (0.726-3.097)	.274	2.335 (1.053-5.180)	.037*
	IIIC vs IB-IIA	2.821 (1.717-4.636)	<.001*	2.227 (1.227-4.041)	.008*	2.298 (1.344-3.929)	.002*	3.222 (1.690-6.143)	<.001*
Invasion depth	>50% vs ≤50%	2.747 (1.446-5.219)	.007*	3.271 (1.344-7.958)	.009*	2.001 (1.043-3.838)	.037*	1.686 (0.811-3.504)	.162
LVSI	Yes vs no	2.108 (1.374-3.234)	.001*	1.973 (1.139-3.417)	.015*	2.370 (1.457-3.854)	.001*	1.705 (1.020-2.851)	.042*
RMI	Yes vs no	1.096 (0.632-1.900)	.745	0.971 (0.470-2.007)	.938	1.158 (0.626-2.143)	.640	0.932 (0.463-1.878)	.844
Adjuvant RT	Yes vs no	0.859 (0.324-2.278)	.760	0.959 (0.249-3.697)	.951	1.016 (0.351-2.944)	.976	1.791 (0.377-8.520)	.464
Adjuvant CCRT	Yes vs no	1.014 (0.375-2.740)	.979	1.489 (0.386-5.735)	.563	1.148 (0.388-3.392)	.803	2.314 (0.480-11.153)	.296

Abbreviations: CCRT = concurrent chemoradiotherapy; CI = confidence interval; DFS = disease-free survival; DMFS = distant metastasis-free survival; FIGO = International Federation of Gynecology and Obstetrics; HPVA = human papillomavirus–associated; HPVI = human papillomavirus–independent; HR = hazard ratio; LRRFS = locoregional recurrence-free survival; LVSI = lymphovascular space invasion; OS = overall survival; RMI = resection margin involvement; RT = radiation therapy.

* Statistically significant.

pathogenesis of clear cell–type HPVI ADC.[24] They found a loss of PTEN, an increase in epidermal growth factor receptor, and an amplification of human epidermal growth factor receptor 2 in more than half of patients with clear cell–type HPVI ADC. The genetic profile of mesonephric-type HPVI ADC is characterized by the activating *KRAS* mutation, which is identified in approximately 80% of cases.[20,25,26] At the chromosomal analysis, 71% of tumors exhibit 1q gain, often accompanied by 1p loss. In addition, 57% of these tumors harbor chromosome 10 gain, frequently associated with chromosome 12 gain.[27-29] Mutations in *FGFR2* and *TP53* are also rarely identified in mesonephric-type HPVI ADCs of the uterine cervix and vagina.[30,31] Based on these distinct molecular features, optimization of CTx regimen for patients with HPVI ADC might be needed. Several studies have suggested the potential benefit of taxane-containing regimen in endocervical ADC.[32,33] Recent research has demonstrated the potential efficacy of PD-1/L1 inhibitors in the treatment of patients with metastatic or recurrent endocervical ADC.[34] The potential advantages of including immunotherapy in adjuvant settings should be looked into, especially in high-risk HPVI ADC.

Higher rates of local recurrence as well as distant metastasis in HPVI ADC than HPVA ADC are notable findings of this study. Although these results needs to be validated in additional studies, high local recurrence rate might be related to high rates of resection margin involvement in HPVI ADC. A previous study reported that the extent of tumor invasion can be underestimated in gastric-type ADC on magnetic resonance imaging, which may result in unintentional incomplete resection.[10] It is suggested that more attention will be needed to secure the surgical margin by generous removal of tumors, particularly in HPVI ADC. Another relevant factor for local recurrence might be radiosensitivity. Several authors have suggested that the endocervical ADC is less sensitive to RT compared to SQC, and that the adjuvant RT is less effective in these patients.[35,36] Further studies will be warranted to determine whether higher radiation doses, additional brachytherapy, or a combination of concurrent systemic therapy could reduce the risk of local recurrence in patients with HPVI ADC.

According to the updated WHO classification, both HPVA and HPVI ADCs are further classified into several histologic types. In HPVA, usual type is the most common, and the mucinous type is divided into intestinal, ISM, signet-ring cell, and NOS categories. In HPVI ADC, the most common is gastric type, and it also includes clear, serous, and mesonephric types. Within HPVA ADC, ISM-type ADC had worse prognosis than other HPVA ADCs. The OS of ISM type was significantly worse than usual type or other mucinous types and similar with that of HPVI ADC (Table E5). Similarly, patients with serous- and gastric-type ADCs exhibited worse survival than those with other HPVI ADC. Although the number of cases is relatively small, there are other previous studies that suggested the aggressive feature and poor prognosis of ISM and gastric type. An international multicenter study analyzed the 52 cases of ISM and

demonstrated that ISM presents with more adverse features and local/distant recurrence than other HPVA ADCs.[37] A recent study by IECC also reported that HPVI ADC (particularly gastric type) and ISM have poor prognosis.[6] In line with these results, we also found that ISM- and gastric-type ADCs had worse survival than other types of HPVA and HPVI ADCs, respectively. Despite the lack of large-scale data, consistent results including our study suggest different prognosis according to the different types within HPVA and HPVI ADC groups.

This study has a drawback of selection bias because of the retrospective nature. There was no difference in imaging evaluation and follow-up of HPVI and HPVA ADCs and multivariate analysis was utilized to control for confounding variables. Nevertheless, this study is one of the largest studies that validated the significant difference in prognosis between HPVI and HPVA ADC, and we further found the distinctive characteristics such as high rates of local recurrence and peritoneal seeding in HPVI ADC.

Conclusion

We demonstrated that HPVI ADC had inferior DFS and OS than HPVA ADC with higher local recurrence and distant metastasis rates. In HPVA ADC, ISM type tend to exhibit worse survival compared to other types. Similarly, gastric and serous types had worse survival than other HPVI ADC types. To improve the treatment outcomes of endocervical HPVI ADC, effective local therapy as well as systemic therapy needs to be further investigated. Different prognosis between types within HPVA and HPVI group needs to be validated with larger number of patients.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021;71:209-249.
2. Hu K, Wang W, Liu X, Meng Q, Zhang F. Comparison of treatment outcomes between squamous cell carcinoma and adenocarcinoma of cervix after definitive radiotherapy or concurrent chemoradiotherapy. *Radiat Oncol* 2018;13:249.
3. Horne ZD, Karukonda P, Kalash R, et al. Single-institution experience in 3D MRI-based brachytherapy for cervical cancer for 239 women: Can dose overcome poor response? *Int J Radiat Oncol Biol Phys* 2019;104:157-164.
4. Yokoi E, Mabuchi S, Takahashi R, et al. Impact of histological subtype on survival in patients with locally advanced cervical cancer that were treated with definitive radiotherapy: Adenocarcinoma/adenosquamous carcinoma versus squamous cell carcinoma. *J Gynecol Oncol* 2017;28:e19.
5. Cree IA, White VA, Indave BI, Lokuhetty D. Revising the WHO classification: Female genital tract tumours. *Histopathology* 2020;76:151-156.
6. Hodgson A, Olkhov-Mitsel E, Howitt BE, Nucci MR, Parra-Herran C. International Endocervical Adenocarcinoma Criteria and Classification (IECC): Correlation with adverse clinicopathological features and patient outcome. *J Clin Pathol* 2019;72:347-353.
7. Hodgson A, Park KJ, Djordjevic B, et al. International endocervical adenocarcinoma criteria and classification: Validation and interobserver reproducibility. *Am J Surg Pathol* 2019;43:75-83.
8. Stolnicu S, Barsan I, Hoang L, et al. International Endocervical Adenocarcinoma Criteria and Classification (IECC): A new pathogenetic classification for invasive adenocarcinomas of the endocervix. *Am J Surg Pathol* 2018;42:214-226.
9. Ren H, Almadani N, Pors J, et al. International Endocervical Adenocarcinoma Criteria and Classification (IECC): An independent cohort with clinical and molecular findings. *Int J Gynecol Pathol* 2021;40:533-540.
10. Park KJ, Kim MH, Kim JK, Cho KS. Gastric-type adenocarcinoma of the uterine cervix: Magnetic resonance imaging features, clinical outcomes, and prognostic factors. *Int J Gynecol Cancer* 2018;28:1203-1210.
11. Jung H, Bae GE, Kim HM, Kim HS. Clinicopathological and molecular differences between gastric-type mucinous carcinoma and usual-type endocervical adenocarcinoma of the uterine cervix. *Cancer Genom Proteom* 2020;17:627-641.
12. Wang W, Liu X, Meng Q, Zhang F, Hu K. Nomograms predicting survival and patterns of failure in patients with cervical cancer treated with concurrent chemoradiotherapy: A special focus on lymph nodes metastases. *PLoS One* 2019;14 e0214498.
13. Yang K, Park W, Huh SJ, Bae DS, Kim BG, Lee JW. Clinical outcomes in patients treated with radiotherapy after surgery for cervical cancer. *Radiat Oncol* 2017;35:39-47.
14. Liu X, Meng Q, Wang W, Zhou Z, Zhang F, Hu K. Predictors of distant metastasis in patients with cervical cancer treated with definitive radiotherapy. *J Cancer* 2019;10:3967-3974.
15. Burg L, Timmermans M, van der Aa M, et al. Incidence and predictors of peritoneal metastases of gynecological origin: A population-based study in the Netherlands. *J Gynecol Oncol* 2020;31:e58.
16. Mileshkin LR, Moore KN, Barnes E, et al. Adjuvant chemotherapy following chemoradiation as primary treatment for locally advanced cervical cancer compared to chemoradiation alone: The randomized phase III OUTBACK trial (ANZGOG 0902, RTOG 1174, NRG 0274). *J Clin Oncol* 2021;39:LBA3.
17. Hodgson A, Howitt BE, Park KJ, Lindeman N, Nucci MR, Parra-Herran C. Genomic characterization of HPV-related and gastric-type endocervical adenocarcinoma: Correlation with subtype and clinical behavior. *Int J Gynecol Pathol* 2020;39:578-586.
18. Cancer Genome Atlas Research N, Albert Einstein College of M, Analytical Biological S. Integrated genomic and molecular characterization of cervical cancer. *Nature* 2017;543:378-384.
19. Hodgson A, Amemiya Y, Seth A, Cesari M, Djordjevic B, Parra-Herran C. Genomic abnormalities in invasive endocervical adenocarcinoma correlate with pattern of invasion: Biologic and clinical implications. *Mod Pathol* 2017;30:1633-1641.
20. Giannella L, Di Giuseppe J, Delli Carpini G, et al. HPV-negative adenocarcinomas of the uterine cervix: From molecular characterization to clinical implications. *Int J Mol Sci.* 2022;23:15022.
21. Park E, Kim SW, Kim S, et al. Genetic characteristics of gastric-type mucinous carcinoma of the uterine cervix. *Mod Pathol* 2021;34:637-646.
22. Stolnicu S, Karpathiou G, Guerra E, et al. Clear cell carcinoma (CCC) of the cervix is a human papillomavirus (HPV)-independent tumor associated with poor outcome: A comprehensive analysis of 58 cases. *Am J Surg Pathol* 2022;46:765-773.
23. Boyd J, Takahashi H, Waggoner SE, et al. Molecular genetic analysis of clear cell adenocarcinomas of the vagina and cervix associated and unassociated with diethylstilbestrol exposure in utero. *Cancer* 1996;77:507-513.
24. Ueno S, Sudo T, Oka N, et al. Absence of human papillomavirus infection and activation of PI3K-AKT pathway in cervical clear cell carcinoma. *Int J Gynecol Cancer* 2013;23:1084-1091.
25. Na K, Kim HS. Clinicopathologic and molecular characteristics of mesonephric adenocarcinoma arising from the uterine body. *Am J Surg Pathol* 2019;43:12-25.
26. Mirkovic J, Sholl LM, Garcia E, et al. Targeted genomic profiling reveals recurrent KRAS mutations and gain of chromosome 1q in mesonephric carcinomas of the female genital tract. *Mod Pathol* 2015;28:1504-1514.

27. Pirog EC. Cervical adenocarcinoma: Diagnosis of human papillomavirus-positive and human papillomavirus-negative tumors. *Arch Pathol Lab Med.* 2017;141:1653-1667.
28. Mirkovic J, McFarland M, Garcia E, et al. Targeted genomic profiling reveals recurrent KRAS mutations in mesonephric-like adenocarcinomas of the female genital tract. *Am J Surg Pathol* 2018;42:227-233.
29. Kim H, Yoon N, Woo HY, et al. Atypical mesonephric hyperplasia of the uterus harbors pathogenic mutation of Kirsten rat sarcoma 2 viral oncogene homolog (KRAS) and gain of chromosome 1q. *Cancer Genom Proteom* 2020;17:813-826.
30. Devarashetty S, Chennapragada SS, Mansour R. Not your typical adenocarcinoma: A case of mesonephric adenocarcinoma of the cervix with fibroblast growth factor receptor 2 (FGFR2) mutation. *Cureus* 2022;14:e25098.
31. Lee H, Kim H, Kim HS. Mesonephric adenocarcinoma of the vagina harboring TP53 mutation. *Diagnostics* 2022;12:119.
32. Nagao S, Fujiwara K, Oda T, et al. Combination chemotherapy of docetaxel and carboplatin in advanced or recurrent cervix cancer. A pilot study. *Gynecol Oncol.* 2005;96:805-809.
33. Kastritis E, Bamias A, Efstathiou E, et al. The outcome of advanced or recurrent non-squamous carcinoma of the uterine cervix after platinum-based combination chemotherapy. *Gynecol Oncol.* 2005;99:376-382.
34. Monk BJ, Enomoto T, Kast WM, et al. Integration of immunotherapy into treatment of cervical cancer: Recent data and ongoing trials. *Cancer Treat Rev* 2022;106 102385.
35. Huang YT, Wang CC, Tsai CS, et al. Long-term outcome and prognostic factors for adenocarcinoma/adenosquamous carcinoma of cervix after definitive radiotherapy. *Int J Radiat Oncol Biol Phys* 2011;80:429-436.
36. Katanyoo K, Sanguanrungsirikul S, Manusirivithaya S. Comparison of treatment outcomes between squamous cell carcinoma and adenocarcinoma in locally advanced cervical cancer. *Gynecol Oncol.* 2012;125:292-296.
37. Stolnicu S, Boros M, Segura S, et al. Invasive stratified mucinous carcinoma (ISMC) of the cervix often presents with high-risk features that are determinants of poor outcome: An international multicenter study. *Am J Surg Pathol* 2020;44:1374-1380.