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Stromal invasion pattern identifies patients at lowest risk of lymph node metastasis in HPV-associated endocervical adenocarcinomas, but is irrelevant in adenocarcinomas unassociated with HPV

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Abstract

Objective: The Silva invasion pattern-based classification system stratifies endocervical adenocarcinomas (ECAs) into 3 categories corresponding to risk of metastasis and recurrence, but has only been evaluated for HPV-associated ECAs of usual type. We examined whether the Silva system is applicable to all endocervical adenocarcinomas, especially those not associated with HPV.

Methods: Complete slide sets from 341 surgical specimens of ECA were collected from 7 institutions worldwide. All specimens were associated with clinical records covering at least 5 years of follow-up. Tumors were classified as HPV-associated (HPVA) or not (NHPVA) by both morphology and detection of HPV using in situ hybridization. Recurrence and survival were analyzed by multivariate Mantel-Haenszel methods.

Results: Most specimens (292; 85.6%) were HPVA, while 49 (14.3%) were NHPVA. All NHPVAs were Silva pattern C, while 76.0% of HPVAs were pattern C, 14.7% pattern A, and 9.3% pattern B. Including both HPVAs and NHPVAs, lymphovascular invasion (LVI) was detected in

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Conflicts of interest

The authors affirm that they have no conflicts of interest related to this research.

0% of pattern A, 18.5% of pattern B and 62.6% of pattern C cases ($p < 0.001$). None of the pattern A or B cases were associated with lymph node metastases (LNM), in contrast to pattern C cases (21.8%). Among patients with Silva pattern C ECA, those with HPVA tumors had a lower recurrence rate and better survival than those with NHPVA; however, when adjusted for stage at diagnosis, the difference in recurrence and mortality was small and not statistically significant.

Conclusions: Application of the Silva system is only relevant in HPVA cervical adenocarcinoma.

Introduction

The management of endocervical adenocarcinoma (ECA) is currently based on FIGO/AJCC staging, taking into account tumor size and extent for visible and/or palpable tumors, or extent/ depth of invasion (DOI) for clinically occult lesions [1]. However, assessing the presence and extent of invasion of clinically occult adenocarcinomas is difficult. Further, lymphovascular invasion (LVI) is not currently part of the staging system, but its presence is an important factor in selecting appropriate surgery [2]. This system has limited reproducibility for staging early adenocarcinomas and may lead to unnecessary radical surgery, which is associated with greater risk of short- and long-term complications than more limited procedures.

To provide a more clinically meaningful means of classifying cervical adenocarcinomas, the Silva invasion pattern-based system was developed in 2013 by reviewing 350 usual-type endocervical adenocarcinomas, separating cases with low risk of metastasis and aggressive behavior (non-destructive pattern A and predominantly non-destructive pattern B without LVI) from cases with higher risk (focally destructive pattern B with LVI and diffusely destructive pattern C) [3]. The Silva system was then validated in subsequent studies, including assessments of inter-observer agreement [4–7]. Treatment modalities for each invasion pattern have been recently proposed [8]: pattern A patients can be safely treated by excision with negative margins, without nodal sampling or adjuvant therapy; pattern B patients' therapy may be individualized based on the presence of LVI; while pattern C patients require lymph node assessment, radical surgery, if applicable, and adjuvant or preoperative therapy [2]. Although the system was originally developed based on conization and radical trachelectomy/hysterectomy specimens, it is anticipated that the Silva system will be applicable to LEEP and conization specimens with negative margins, which could improve treatment planning [8].

A criticism of the Silva system is that it was developed by studying only usual-type adenocarcinomas, all of which are associated with HPV. One possible explanation for this is the rarity of non-HPV-associated ECAs, which have only recently been recognized [9, 10]. Indeed, the impact of etiology on outcomes—non-HPV-associated adenocarcinomas (NHPVAs) are more likely to metastasize and have worse survival than HPV-associated adenocarcinomas (HPVAs) [9, 11, 12]—led to the development of a method of distinguishing NHPVA from HPVA based on morphology [13]. The aim of this study was to evaluate Silva invasion patterns in all histological subtypes of HPVAs and NHPVAs and to examine their relationship with clinical outcomes.

Materials and methods

Patient selection

Complete slide sets from 367 resected ECAs from 7 institutions worldwide were collected, each of which was accompanied by records detailing at least 5 years of follow-up. Institutional IRBs approved the study. In situ carcinomas, squamous carcinomas, adenosquamous carcinomas, tumors with a neuroendocrine component, carcinosarcomas, and any tumor demonstrating clinical, macroscopic or microscopic features suggesting a lower uterine segment, uterine corpus, or adnexal primary were excluded. Specimens collected via therapeutic loop electrosurgical excision procedures (LEEPs), conizations, trachelectomies, or hysterectomies (all accompanied by lymph node dissection) were included, while biopsies and LEEP without lymph node sampling were excluded. Patients treated with chemotherapy and/or radiotherapy prior to surgery were also excluded. Patient age and tumor diameter were recorded in each case. Of these cases, 341 were successfully categorized as Silva A, B, or C (see below).

Morphological assessment

All microscopic subtypes of ECA were included, and all H&E slides on which tumor tissue was present (average of 12 slides per case) were morphologically assessed. A consensus diagnosis was reached in every case, with at least 2 and as many as 4 study pathologists reviewing slides at a multi-head microscope. Cases were classified according to the International Endocervical Adenocarcinoma Criteria and Classification (IECC) system (Table 1) [13].

Categorization as HPVA or NHPVA was confirmed by detection of HPV, using the Advanced Cell Diagnostics (Hayward, CA) RNAscope® chromogenic HPV in-situ hybridization assay (catalogue no. 312598). The RNAscope® Probe HPV HR18 contains probes targeting E6 and E7 mRNA for the following high-risk subtypes: HPV16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73 and 82. Tumors known to contain high-risk HPV (HR-HPV) were used as positive controls, while those known to be HR-HPV-negative were used as negative controls during assay optimization. Subsequently, a negative control slide to which the probes were not applied was prepared and examined, particularly when adjudicating cases with rare or equivocal signals. A full range of cytoplasmic and nuclear signals were encountered as previously described [14].

Specimens were subsequently categorized as Silva A, B or C. Silva pattern A tumors were composed of well-demarcated glands with rounded contours, frequently forming groups. Specimens with destructive stromal invasion, single cells or cell detachment with paradoxical maturation, LVI or solid growth were excluded from this classification, but complex intraglandular growth (cribriform or papillae) was accepted if it was less than 5 mm in greatest dimension. Pattern B carcinomas consisted of localized or “limited” destructive stromal invasion in a background of pattern A, where limited destructive invasion was defined by individual or small groups of tumor cells in a focally desmoplastic stroma with an inflammatory infiltrate. Destructive foci were single or multiple, each measuring less than 5 mm in diameter. LVI was acceptable in pattern B, but solid growth was not. Pattern C

ECAs featured diffuse destructive stromal invasion by infiltrating glands associated with a desmoplastic stromal response. Glands were often angulated or fragmented. Some pattern C tumors displayed LVI, solid, poorly differentiated, architecturally high-grade components, or confluent growth (glands, papillae or mucin lakes) filling a 4× field (>5 mm) [3].

The presence of LVI, lymph node metastases (LNM), and micropapillary components (defined as nests of cells with abundant eosinophilic cytoplasm and surrounded by an empty space, representing at least 10% of the tumor) were recorded in each case.

Statistical analysis

We used standard Kaplan-Meier methods for recurrence and survival analysis in the statistical package program STATA 13 (StataCorp, College Station, TX). Factors associated with recurrence or survival were analyzed using the log-rank test, and overall hazard ratios were estimated using the method described by Pike [15]. Factors were adjusted for other factors using the log-rank method with stratification according to the adjustment factor, allowing estimation of adjusted overall hazard ratios. All analyses were stratified by the site/institution at which patients were treated. Recurrence and survival curves were adjusted by power transformation using the adjusted overall hazard ratio of the baseline comparison curve.

Results

Within our sample set, HPVA was more frequent and histologically diverse (according to both WHO and Silva pattern) than NHPVA (Table 2). Of the 341 classifiable ECA cases, 85.6% (n=292) were HPVA (88.7% usual, 3.4% mucinous NOS, 3.1% intestinal, 3.1% invasive stratified mucin-producing intraepithelial lesions (iSMILE), 1.7% adenocarcinoma NOS), while 49 cases (14.4%) were NHPVA (67.3% gastric, 12.2% clear cell, 8.2% adenocarcinoma NOS, 6.1% endometrioid, 4.1% serous, 2.0% mesonephric) (Table 2). Among the NHPVA cases, 100% were pattern C, while HPVA cases included all 3 patterns: 76.0% pattern C, 14.7% pattern A, and 9.3% pattern B (Table 2).

NHPVAs were larger and more frequently invasive and metastatic than HPVAs (Table 3). The median size of HPVAs was 21 mm, compared with 40 mm for NHPVAs ($p < 0.001$). Including both HPVAs and NHPVAs, lymphovascular invasion (LVI) was detected in 0% of pattern A, 18.5% of pattern B, and 64.6% of pattern C cases ($p < 0.001$). LVI was more frequently seen in NHPVAs (73.5% vs. 49.3% of HPVAs; $p = 0.006$), even when compared only with HPVA pattern C cases (62.6%). Similarly, NHPVAs were more frequently associated with LNM (30.6% vs. 15.1% of HPVAs; $p = 0.009$). None of the pattern A and B cases were associated with LNM, in contrast to pattern C (19.8% of HPVA cases). Among HPVA pattern C cases, stage ($p < 0.001$), LVI (p adjusted for stage = 0.001) and tumor size (p adjusted for stage = 0.002) were associated with lymph node metastasis.

Because NHPVAs could not be risk-stratified by invasion pattern (all had pattern C invasion), we sought to determine which features were associated with risk of LNM by multivariate analysis. Among patient age, tumor size, stage, histotype, presence of LVI and presence of a micropapillary component, stage was the only factor significantly associated

with LNM ($p < 0.001$). LVI was also associated with LNM, but the relationship was no longer statistically significant after adjustment for stage ($p=0.10$). As 3 of 26 stage 1 NHPVAs had an LNM, there was no cutoff stage below which no LNM would be expected. Silva pattern C HPVAs had a lower recurrence rate and better survival than Silva C NHPVAs, but when adjusted for stage, the differences in recurrence and mortality were small and not statistically significant (Table 4, Figure 1).

Discussion

The Silva morphologic classification system categorizes ECAs into 3 patterns based on indicators of invasion; these patterns predict risk of lymph node metastasis more accurately than clinical stage [3, 6, 8]. The system was developed to avoid unnecessary lymphadenectomy and attendant morbidity for lowest-risk patients, irrespective of stage. As the Silva system had not yet been applied to uncommonly encountered HPVAs or any NHPVAs, we examined the feasibility and relevance of applying it to both HPVAs and NHPVAs, and evaluated clinical-pathological features that influence outcomes in NHPVAs. We found that all NHPVAs display the same Silva pattern (C, the most invasive) and that their risk of metastasis depends only on clinical stage, so this system is not useful in their evaluation.

In general, our data concerning HPVAs agree with the findings of other studies. We observed a similar prevalence of LNM to that reported in the original paper describing the Silva system (0% vs. 0% for pattern A; 0% versus 4% for pattern B; and 24% versus 22% for pattern C, respectively) [3]. However, we saw a higher prevalence of pattern C HPVAs than in the original series (76% vs. 53%), the reason for which is uncertain.

Our finding that increasing tumor size and the presence of LVI correlate with LNM in HPVAs pattern C cases also confirms prior literature. In a study of locally advanced ECA, the frequency of LNM was found to be higher among patients with tumors larger than 4 cm in diameter compared with patients with smaller tumors [16]. In a study of usual-type pattern C HPVAs, LNM was more frequent as tumor size increased over 35 mm diameter [7]. The same study also reported that in the presence of LVI, 23% of patients had LNM, compared with only 3% among those whose tumors lacked LVI. Moreover, the extent of LVI (more than 20 LVI spaces) was an independent predictor of LNM and was strongly associated with recurrence and distant metastasis [7]. Pattern C HPVAs with LVI and LNM have also been associated with higher recurrence rates and worse survival compared with pattern C tumors without LVI or LNM [8].

Not only were all NHPVAs studied pattern C (compared with only 76.0% of HPVAs), but these ECAs were also larger and more frequently associated with LVI and LNM. However, only small numbers of endometrioid, serous, mesonephric and NOS NHPVAs were available for study, so further study of these uncommon subtypes is needed to confirm that they always display this invasion pattern. On multivariate analysis including age, FIGO stage, tumor size, LVI, micropapillary architecture and histotype, FIGO stage was the only parameter that was statistically significantly associated with LNM. Unlike pattern A and B

HPVAs, which were not associated with LNM in this study, 11.5% of FIGO stage I NHPVAs were associated with LNM and all these cases had LVI present.

Though we used HR-HPV in situ hybridization (ISH) to confirm classification as HPVA or NHPVA, this approach is not required. Our ISH results agreed with those of the IECC morphological system, so examination of H&E slides should be sufficient to distinguish between HPVAs and NHPVAs in most cases. When categorization is challenging, HR-HPV ISH (if available) or detection of the less sensitive and specific marker p16 could be employed.

In conclusion, although it is feasible to assign Silva pattern to all endocervical adenocarcinomas irrespective of HPV-mediated etiology, clinical outcomes in NHPVAs are driven primarily by stage at diagnosis. Appropriate clinical algorithms should be developed that include classifying ECAs into HPV-positive and -negative cases, accounting for Silva pattern in the former and FIGO stage in the latter.

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Figure 1. Observed survival (A) and recurrence (B) of patients with Silva pattern C endocervical adenocarcinoma. Adj. NHPVA, adjusted to match the stage distribution of HPVA patients.

Table 1.

IECC criteria for classification of endocervical adenocarcinomas.

Major classification	Tumor subtype	Morphologic features
HPVA (Apical mitotic figures and apoptotic bodies appreciable at scanning magnification)	Usual	0–50% of cells with appreciable intracytoplasmic mucin, +/- squamous differentiation
	Mucinous NOS	50% of cells with intracytoplasmic mucin in a background of usual-type
	Mucinous intestinal	50% of cells with goblet morphology in a background of usual-type
	Mucinous signet-ring	50% of tumor cells with signet-ring morphology in a background of usual-type
	Invasive SMILE	Invasive nests of stratified columnar cells with peripheral palisading and variable amounts of intracytoplasmic mucin
	Villoglandular	Usual-type cytomorphology with exophytic long slender papillae
NHPVA (No easily identifiable mitotic activity or apoptotic bodies at scanning magnification, focal/equivocal HPVA features appreciable at 200×, or “limited HPVA” features)	Gastric	Cells with abundant clear, foamy or pale eosinophilic cytoplasm, distinct cytoplasmic borders, generally low nuclear-to-cytoplasmic ratios and irregular basally located nuclei, +/- HPVA-like features
	Clear cell	Solid, papillary and/or tubulocystic architecture with polygonal cells and highly atypical but uniform nuclei
	Endometrioid	Endometrioid morphology with “confirmatory features” (at least focally identified low-grade endometrioid glands lined by columnar cells, with pseudostratified nuclei demonstrating no more than moderate atypia, +/- squamous differentiation and/or endometriosis present)
	Serous	Papillary and/or micropapillary architecture with cells showing diffusely distributed, highly atypical nuclei in stratified and pseudostratified cells
	Mesonephric	Admixture of growth patterns (ductal, tubular, papillary, cord-like and others) as well as intraluminal eosinophilic colloid-like material resembling mesonephric remnants
	Adenocarcinoma NOS	Any tumor not meeting criteria for any other IECC subtype

SMILE, stratified mucin-producing intraepithelial lesions.

Table 2.

Distribution of endocervical adenocarcinomas according to IECC subtype and Silva pattern.

Subtype	HPVA			Total	NHPVA Silva C
	Silva A n (%) ^a	Silva B n (%) ^a	Silva C n (%) ^a		
Usual	38 (14.7)	24 (9.3)	197 (76.1)	259	
Gastric					33
Mucinous NOS		1 (10.0)	9 (90.0)	10	
Mucinous intestinal	3 (33.3)	2 (22.2)	4 (44.4)	9	
Mucinous signet-ring					
Clear cell					6
iSMILE	1 (11.1)		8 (88.9)	9	
Adenocarcinoma NOS	1 (20.0)		4 (80.0)	5	4
Endometroid					3
Villoglandular					
Serous					2
Mesonephric					1
Total	43 (14.7)	27 (9.3)	222 (76.0)	292	49

^a% of HPVA subtype.

iSMILE, invasive stratified mucin-producing intraepithelial lesions.

Table 3.

Invasion, lymph node metastasis, size, and stage of endocervical adenocarcinomas according to HPVVA classification and Silva pattern.

	Silva pattern	LVI ^a	LNM ^a	Size (mm) ^b	Stage				
					1	2	3	4	ND
HPVA	A (n=43)	0 (0)	0 (0)	14	40 (93)	2 (4.7)			1 (2.3)
	B (n=27)	5 (18.5)	0 (0)	10	25 (92.6)				2 (7.4)
	C (n=222)	139 (62.6)	44 (19.8)	25	181 (81.5)	19 (8.6)	6 (2.7)	1 (0.5)	15 (6.8)
NHPVA	Any (n=292)	144 (49.3)	44 (15.1)	21	246 (84.2)	21 (7.2)	6 (2.1)	1 (0.3)	18 (6.2)
	C (n=49)	36 (73.5)	15 (30.6)	40	21 (42.8)	19 (38.8)	3 (6.1)	1 (2.0)	5 (10.2)
HPVA or NHPVA	C (n=271)	175 (64.6)	59 (21.8)	27	202 (74.5)	38 (14.0)	9 (3.3)	2 (0.7)	20 (7.4)
All	Any (n=341)	180 (52.8)	59 (17.3)	24	267 (78.3)	40 (11.7)	9 (2.6)	2 (0.6)	23 (6.7)

^aPercentage positive;

^bmedian of available values (31 specimens of HPVVA Silva A, 21 HPVVA Silva B, 199 HPVVA Silva C, 35 NHPVA).

LVI, lymphovascular invasion; LNM, lymph node metastasis; ND, no data.

Table 4.

Recurrence and mortality of patients with Silva pattern C endocervical adenocarcinoma.

Recurrence						
	Patients	Observed	Recurrences			
			Expected^a	Hazard ratio	Adjusted expected^b	Adjusted HR^b
HPVA	159	33	39.0		34.7	
NHPVA	28	15	9.0	2.0	13.3	1.2
				(1.1 – 3.3)		(0.7 – 1.9)
				p = 0.014		p = 0.48
Mortality						
	Patients	Observed	Deaths			
			Expected^a	Hazard ratio	Adjusted expected^b	Adjusted HR^b
HPVA	164	19	23.8		19.8	
NHPVA	27	11	6.2	2.2	10.2	1.1
				(1.2 – 4.3)		(0.6 – 2.0)
				p = 0.016		p = 0.72

^aExpected number adjusting for site and time on study, assuming no relation to HPVA/NHPVA;^bAdjusted for stage of disease.