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Improved Risk Prediction in Human Papillomavirus–Associated Endocervical Adenocarcinoma Through Assessment of Binary Silva Pattern-based Classification: An International Multicenter Retrospective Observational Study Led by the International Society of Gynecological Pathologists (ISGyP)

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Abstract: Endocervical adenocarcinomas (EACs) are a group of malignant neoplasms associated with diverse pathogenesis, morphology, and clinical behavior. As a component of the International Society of Gynecological Pathologists International Endocervical Adenocarcinoma Project, a large international retrospective cohort of EACs was generated in an effort to study potential clinicopathological features with prognostic significance that may guide treatment in these patients. In this study, we endeavored to develop a robust human papillomavirus (HPV)–associated EAC prognostic model for surgically treated International Federation of Gynecology and Obstetrics (FIGO) stage IA2 to IB3 adenocarcinomas incorporating patient age, lymphovascular space invasion (LVSI) status, FIGO stage, and pattern of invasion according to the Silva system (traditionally a 3-tier system). Recently, a 2-tier/binary Silva pattern of invasion system has been proposed whereby adenocarcinomas are classified into low-risk (pattern A/pattern B without LVSI) and high-risk (pattern B with LVSI/pattern C) categories. Our cohort comprised 792 patients with HPV-associated EAC. Multivariate analysis showed that a binary Silva pattern of invasion classification was associated with recurrence-free and disease-specific survival ($P < 0.05$) whereas FIGO 2018 stage I substages were not. Evaluation of the current 3-tiered system showed that disease-specific survival for those patients with pattern B tumors did not significantly differ from that for those patients with pattern C tumors, in contrast to that for those patients with pattern A tumors. These findings underscore the need for prospective studies to further investigate the prognostic significance of stage I HPV-associated EAC substaging and the inclusion of the binary Silva pattern of invasion classification (which includes LVSI status) as a component of treatment recommendations.

Key Words: Endocervical adenocarcinoma, HPV, Pattern-based classification system, Silva pattern, Prognosis, Survival

(*Int J Gynecol Pathol* 2024;43:436–446)

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Pavel Dundr reports funding from the Ministry of Health, Czech Republic. Andrea Palicelli and Magda Zanelli report partial funding support from the Italian Ministry of Health-Ricerca Corrente Annual Program 2023.

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The authors declare no conflict of interest.

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DOI: 10.1097/PGP.0000000000001033

Worldwide, the real and relative incidence of endocervical adenocarcinoma (EAC) has steadily increased[1–4] and these tumors now represent up to 25% of all cervical carcinomas in western countries. Recent studies have greatly enhanced our knowledge and understanding of EAC etiol-

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ogy/pathogenesis, behavior, and management,[5–13] and much of this information is now incorporated in the latest EAC World Health Organization classification, which includes integration of human papillomavirus (HPV) status,[14] updated International Federation of Obstetrics and Gynecology (FIGO) 2018 staging,[15,16] and utilization of the Silva pattern of invasion to assist in the refinement of EAC prognostication.[17] The first 2 of these are well accepted in the pathologic reporting of EACs but the Silva pattern of invasion has not been consistently adopted as no worldwide studies have yet been performed.

To support the adoption of these significant changes, the International Society of Gynecological Pathologists (ISGyP) established an expert "working group" to improve the pathologic reporting of EACs and encourage evidence-based translation into clinical management.[18,19] The working group has delivered a multifaceted project that collated the broad spectrum of current practices in the membership of ISGyP regarding EAC pathologic evaluation and reporting[20] and, in addition, an educational online training course[21] was developed to encourage worldwide consistent histologic reporting of EAC, including application of the Silva pattern of invasion system.

The final component of the EAC working group's major project was to establish an international and real-world EAC, HPV-associated and HPV-independent, data set to investigate specific factors associated with disease recurrence and disease-specific survival (DSS) in 2 projects: 1) patients with early-stage HPV-associated EACs (presented herein), and 2) similarities and differences between HPV-associated and HPV-independent EACs (to be presented in an upcoming manuscript).

This first study of the working group looking at early-stage HPV-associated EACs aims to provide new evidence on the clinical significance of the Silva pattern of invasion and further develop a robust prognostic model that includes patient age, lymphovascular space invasion (LVSI) status, FIGO stage, and the Silva pattern of invasion as main parameters. The Silva pattern is an important addition to other prognostic clinicopathologic parameters as it categorizes EACs based on the morphologic pattern of invasion rather than the depth of stromal invasion, as the latter can be challenging to measure accurately for a variety of reasons including lack of a defined epithelial-stromal junction/basement membrane in the endocervix and difficulties in distinguishing florid *in situ* from invasive adenocarcinoma.[22,23] The classic system is 3-tiered (Fig. 1, Table 1); however, recent work has suggested that the utilization of a 2-tier (binary) system with an emphasis on the presence or absence of LVSI (high and low-risk tumors) may be more clinically relevant.[24] A biological foundation supporting the latter classification has also been recently described.[25] Herein, we report the results obtained from the ISGyP EAC data set, investigating EAC prognostic models to determine the risk of disease recurrence and DSS in these tumors.

MATERIALS AND METHODS

The ISGyP established an international multicenter consortium to pool individual de-identified patient data for patients with EAC.[18,19] All participating pathologists (see note at end of article) completed mandatory online training (http://www.gpecdata.med.ubc.ca/images/aperio/eac2/)[21] to ensure a consistent approach to the application of the histologic and Silva pattern of invasion classifications for tumors included in the cohort.

This study was sponsored by Queen Mary University of London and ethical approval was provided by the Southwest-Frenchay Research Ethics Committee (reference number: 20/SW/0008). The de-identified data were securely transferred for statistical analysis to the Institute for Health Research, University of Notre Dame Australia, Western Australia (Human Research Ethics Committee reference number: 2020-188F). Principal investigators at individual study sites obtained local and country-specific approvals.

Patient and Tumor Selection

Pathologists at the contributing centers identified patients with histologically confirmed EAC. All glass slides were reviewed by the contributing pathologists and comprised material from excisional biopsies (cold knife cone biopsy or loop electrosurgical excision procedure), trachelectomy, and/or hysterectomy specimens. A comprehensive data collection tool/template was distributed to all contributors to collect the following variables (from slide review and institutional records): patient age at diagnosis, date of diagnosis, FIGO stage (2018), International Endocervical Adenocarcinoma Criteria and Classification/World Health Organization 2020 tumor type,[14] tumor grade (where applicable), Silva pattern of invasion (i.e. pattern A, B, or C), HPV status, surgical procedure(s), presence or absence of LVSI, pelvic lymph node status, date of recurrence (if any), and outcomes. Data discrepancies (corrupted or incorrectly formatted entries) were resolved by consensus and arbitration by a panel of investigators (A.P., A.H., P.A.C., and N.S.).

Study Inclusion and Exclusion Criteria

To specifically study EAC prognostic models to determine the risk of disease recurrence and DSS in these tumors, the study eligibility criteria included patients ≥ 18 years of age with confirmed FIGO stages IA2 to IB3 HPV-associated EAC who had undergone surgical treatment including lymph node dissection. FIGO stage I disease is tumor confined to the cervix (extension to the uterine corpus should be disregarded) and the definitions of the FIGO stage I substages included in the study were as follows: IA2 with measured stromal invasion >3 mm and ≤ 5 mm in depth (diagnosed only by microscopy), IB1 with >5 mm depth of stromal invasion and ≤ 2 cm in greatest dimension, IB2 >2 cm and ≤ 4 cm in greatest dimension, and IB3 >4 cm in greatest dimension. Hematoxylin and eosin-stained (or equivalent) slides

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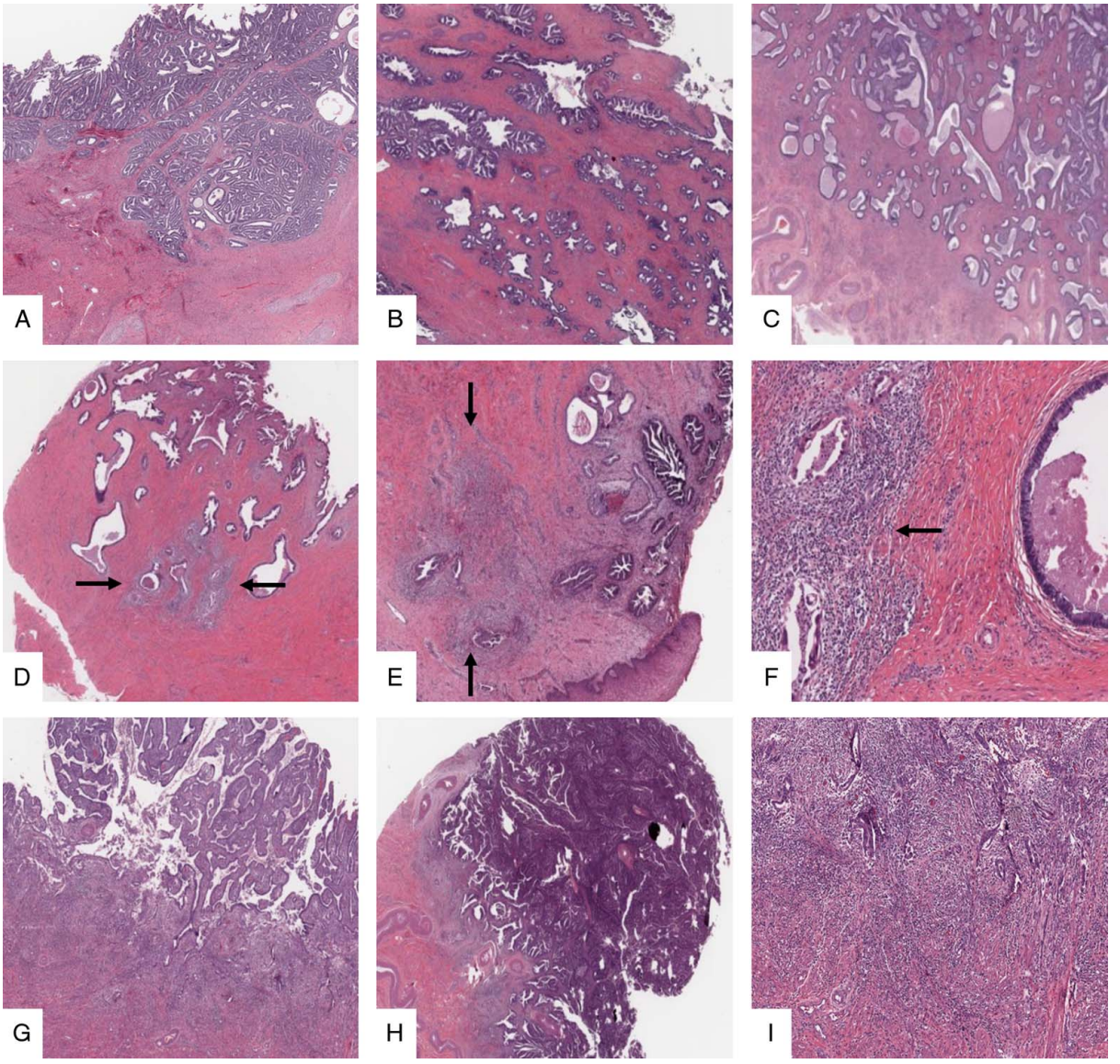

FIGURE 1. Patterns of invasion in HPV-associated EAC. Pattern A tumors are composed of well-formed glands, often with rounded contours with a pushing or infiltrative pattern but without stromal response (A–C). Pattern B tumors show early and limited destructive invasion seen as individual or small clusters of tumor cells or ill-formed glands, often in a desmoplastic, edematous, or inflamed stroma (black arrows) arising from pattern A (D–F). Pattern C tumors typically show poorly formed and diffusely infiltrative glands with associated extensive desmoplastic response but also may display confluent cribriform or papillary growth and an otherwise solid or poorly differentiated component (G–I). Images captured from cases utilized in ISGyP's EAC training and test sets. EAC, endocervical adenocarcinoma; HPV, human papillomavirus; ISGyP, International Society of Gynecological Pathologists.

needed to be available for local review, and a minimum of 1 month of follow-up was required. The pathologic variables, including HPV status and Silva pattern of invasion, were determined by the ISGyP member contributing the case, based on published criteria (described in the online training). Patients were excluded from the study if the tumor was confirmed as 1) HPV-independent or adenosquamous histology, 2) uncertain origin or metastasis to the cervix, or 3) the Silva pattern of invasion could not be assigned.

Statistical Analyses

Statistical analyses were performed using Stata version 17.0 (StataCorp, College Station, TX). Statistical significance was determined as a P value <0.05 for all statistical tests. Differences between the Silva pattern of invasion categories were analyzed using Pearson χ^2 and Fisher exact tests. The 3-tier (pattern A vs B vs C), 4-tier (pattern A vs pattern B without LVSI vs pattern B with LVSI vs pattern C), and 2-tier/binary (pattern A and pattern B without LVSI [low risk] vs pattern B with LVSI

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TABLE 1. Pattern-based/Silva Classification of HPV-associated EAC

Silva pattern	Morphologic features
Pattern A (nondestructive invasion)	Well-demarcated glands with rounded contours, commonly forming groups No solid growth (but complex cribriform or papillary growth $<4\times$field/5 mm acceptable) No single cells/cell detachment No LVSI
Pattern B (early/focal destructive invasion)	Limited/early destructive invasion in the form of individual cells or small groups with associated inflamed/desmoplastic stroma in a background of pattern A glands (single or multiple foci or linear at base of the tumor <4x field/5 mm), +/− LVSI
Pattern C (diffusely destructive invasion)	Diffuse destructive invasion in the form of angulated and often interconnected infiltrative glands with associated inflamed/desmoplastic stroma Linear destructive component at base of tumor ≥ 5 mm or superficial band-like inflammation infiltrate that obscures tumor-stroma interface Solid/sheet-like architecture, micropapillary or otherwise confluent growth (filling a 4x field/5 mm) of glands, papillae or mucin lakes +/− LVSI

EAC, endocervical adenocarcinoma; HPV, human papillomavirus; LVSI, lymphovascular space invasion.

and pattern C [high risk]) Silva classification systems were specifically assessed. The primary outcomes were recurrence-free survival (RFS) and DSS. Recurrence could be local (vaginal), locoregional (pelvic, not including the vagina), distant (outside the pelvis), nodal (pelvic or non-pelvic), or a combination, and the date of recurrence was defined based on a pathologic and/or radiologic report. DSS was defined as death related to EAC and was calculated from the date of index surgical treatment to the date of EAC-related death or the date of last known follow-up. The probability of disease recurrence and DSS were obtained using Fine and Gray univariate (unadjusted) and multivariate (adjusted for patient age, FIGO stage, and the Silva pattern classification) competing risk models to determine the subdistribution hazard ratios (sHRs).[26] The results are presented as sHR and 95% confidence intervals (CI). Competing risk analyses were used to account for the potential imbalance observed in standard Cox regression when patients were lost to follow-up and/or those who died of non-cancer causes (or not the cancer of interest).

RESULTS

The clinicopathological findings of the cohort are summarized in Table 2. Patient data was contributed by 72 institutions where ISGyP members work. Overall, 792 patients were eligible for the study (Fig. 2), with a median follow-up of 4.4 years (range: 2 mo–32 y), including 112 (14.1%) patients with stage IA2, 398 (50.3%) with IB1, 233 (29.4%) with IB2, and 49 (6.2%) with IB3 tumors, respectively. A total of 582 (73.5%) patients were younger than 50 years at the time of diagnosis. Most (742, 93.7%) EAC were of the usual type ($<50\%$ of cells with appreciable intracytoplasmic mucin), whereas the remaining 50 (6.3%) showed predominant mucinous differentiation (intestinal type, not otherwise specified type, or signet-ring cell type). The median depth of invasion was 6 mm (range: 0.5–27 mm), and LVSI was identified in 184 (23.2%) tumors. Of the 792 patients, 73 (9.2%) had recurrence, 18 (2.3%) died from disease, and 5 (0.6%) died from unrelated causes. Of the 73 recurrences, 45 (61.6%) were local/pelvic (Table 3) and, therefore, potentially salvageable.

The univariate (unadjusted) analyses investigating RFS and DSS are presented in Table 4. The risk of disease recurrence was significantly lower for patients younger than 50 years (sHR: 0.71, 95% CI: 0.52–0.96, $P = 0.026$) and with FIGO stage IA2 tumors (sHR: 0.28, 95% CI: 0.87–0.94, $P = 0.039$). In addition, different tier arrangements of the Silva system showed that patients with tumors classified as patterns A and B (3-tier) and A and B with no LVSI (4-tier and 2-tier) also had improved RFS. The presence of LVSI was associated with an increased risk of disease recurrence (sHR: 2.42, 95% CI: 1.74–3.37, $P < 0.001$).

No significant differences in DSS were observed with regard to patient age or FIGO stage. The univariate factors associated with significantly improved DSS included pattern A disease (3-tier and 4-tier systems [sHR: 0.14, 95% CI: 0.39–0.51, $P = 0.003$]) and absence of LVSI (i.e. pattern A and B without LVSI; 2-tier system [sHR: 0.22, 95% CI: 0.07–0.63, $P = 0.005$]).

The multivariate (adjusted) analyses for disease recurrence and DSS are presented in Tables 5–7.

Three-tier Classification

In this model, pattern A (sHR: 0.36, 95% CI: 0.16–0.82, $P = 0.016$) and pattern B (sHR: 0.55, 95% CI: 0.31–0.98, $P = 0.042$) EAC were significantly less likely to recur when compared with pattern C tumors. Of note, the presence of LVSI also portended an increased risk of recurrence (sHR: 1.83, 95% CI: 1.24–2.72, $P = 0.003$). Furthermore, patients with pattern A tumors were less likely to die of disease (sHR: 0.32, 95% CI: 0.13–0.79, $P = 0.013$) when compared to patients with pattern C tumors. The presence of LVSI was also noted to be a significant risk factor for DSS (sHR: 3.91, 95% CI: 1.52–10.08, $P = 0.005$). Patient age less than 50 years and FIGO stage IA2 disease remained significantly associated with RFS but age and FIGO stage were not significantly associated with DSS (Table 5).

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TABLE 2. Characteristics of the Study Cohort (n = 792), Stratified by Silva Pattern of Invasion

Characteristic	Silva pattern of invasion				
	Pattern A (n = 198); n (%)	Pattern B (no LVSI; n = 195); n (%)	Pattern B (+ LVSI; n = 65); n (%)	Pattern C (n = 334); n (%)	*P*
Age (yr)					
< 50	149 (75.3)	151 (77.4)	56 (86.2)	226 (67.7)	0.005
≥ 50	49 (24.7)	44 (22.6)	9 (13.8)	108 (32.3)	—
FIGO stage					
IA2	49 (24.8)	34 (17.4)	7 (10.8)	22 (6.6)	—
IB1	107 (54.0)	106 (54.4)	32 (49.2)	153 (45.8)	0.000
IB2	36 (18.2)	48 (24.6)	22 (33.9)	127 (38.0)	—
IB3	6 (3.0)	7 (3.6)	4 (6.1)	32 (9.6)	—
IECC/WHO tumor type					
HPV adenocarcinoma, usual type	189 (95.4)	188 (96.4)	58 (89.2)	307 (91.2)	0.053
HPV adenocarcinoma, mucinous intestinal type	9 (4.6)	5 (2.6)	5 (7.7)	21 (6.3)	—
HPV adenocarcinoma, mucinous NOS type	—	2 (1.0)	2 (3.1)	2 (0.6)	—
HPV adenocarcinoma, mucinous signet-ring cell type	—	—	—	4 (1.2)	—
Tumor grade					
G1	153 (77.3)	87 (44.6)	19 (29.2)	68 (20.4)	0.000
G2	43 (21.7)	94 (48.2)	41 (63.1)	222 (66.5)	—
G3	1 (0.5)	4 (2.1)	3 (4.6)	37 (11.0)	—
Not reported	1 (0.5)	10 (5.1)	2 (3.1)	7 (2.1)	—
Lymphovascular invasion status					
Absent	198 (100)	195 (100)	—	215 (64.4)	0.000
Present	—	—	65 (100)	119 (35.6)	—
Most extensive surgery performed					
Excisional biopsy (CKC or LEEP)	2 (1.0)	2 (1.0)	—	2 (0.6)	0.016
Trachelectomy	15 (7.6)	20 (10.3)	8 (12.3)	20 (6.0)	—
Extrafascial hysterectomy (± BSO)	20 (10.1)	15 (7.7)	—	14 (4.2)	—
Radical hysterectomy (± BSO)	161 (81.3)	158 (81.0)	57 (87.7)	298 (89.2)	—
Recurrence					
Yes	7 (3.5)	12 (6.2)	6 (9.2)	48 (14.4)	0.000
No	191 (96.5)	183 (93.8)	59 (90.8)	286 (85.6)	—
Outcome					
Alive	194 (98.0)	192 (98.5)	62 (95.4)	321 (96.1)	0.041
Died of disease	1 (0.5)	2 (1.0)	3 (4.6)	12 (3.6)	—
Died of unrelated causes*	3 (1.5)	1 (0.5)	—	1 (0.3)	—

*Died of unrelated causes data excluded from the Fisher exact test.

BSO, bilateral salpingo-oophorectomy; CKC, cold knife cone; FIGO, International Federation of Gynecology and Obstetrics; HPV, human papillomavirus; IECC, International Endocervical Adenocarcinoma Criteria and Classification; LEEP, loop electrosurgical excision procedure; LVSI, lymphovascular space invasion; NOS, not otherwise specified; WHO, World Health Organization.

Four-tier Classification

In this model, patients with tumors showing pattern A (sHR: 0.28, 95% CI: 0.13–0.62, $P = 0.002$) and pattern B without LVSI (sHR: 0.47, 95% CI: 0.23–0.96, $P = 0.038$) were less likely to have recurrences than those with pattern C tumors. Patients with pattern A EAC were significantly less likely to die of disease (sHR: 0.17, 95% CI: 0.06–0.45, $P < 0.001$) compared to patients with pattern C tumors. Of note, pattern B tumors with LVSI were not associated with improved RFS and DSS compared to pattern C tumors (sHR: 0.7, 95% CI: 0.30–1.64, $P = 0.419$ and sHR: 1.29, 95% CI: 0.30–5.57, $P = 0.729$, respectively). Patient age less than 50 years and FIGO stage IA2 disease remained significantly associated with RFS but age and FIGO stage were not significantly associated with DSS (Table 6).

Two-tier Classification

In this model, 54 (74%) of the recurrences and 15 (83%) deaths occurred in patients with high-risk tumors. Importantly, patients with low-risk tumors were significantly less likely to have a recurrence (sHR: 0.40, 95% CI: 0.24–0.65, $P < 0.001$) or die of disease (sHR: 0.25, 95% CI: 0.08–0.77, $P = 0.016$) than those with high-risk tumors. Patient age less than 50 years remained significantly associated with RFS, but age and FIGO stage were not significantly associated with DSS (Table 7).

DISCUSSION

To the best of our knowledge, this is the largest reported study on HPV-associated EAC. We found that a 2-tier/binary Silva pattern of invasion classification that incorporates LVSI status more accurately predicts RFS and DSS compared to FIGO substage in stage I tumors, and also compared to the traditional 3-tier Silva pattern system. We built robust statistical models to investigate prognostic factors associated with disease recurrence and death. Patient age, FIGO stage, LVSI status, and different Silva

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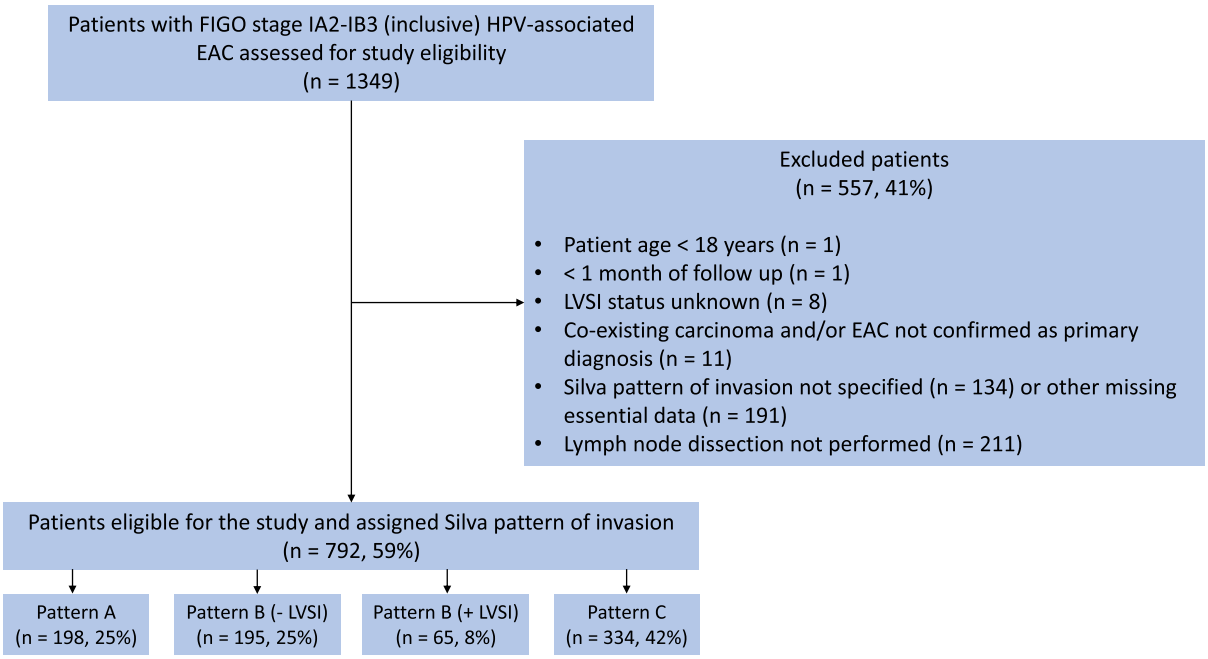

FIGURE 2. Final cohort selection and reasons for exclusion. EAC, endocervical adenocarcinoma; FIGO, International Federation of Gynecology and Obstetrics; HPV, human papillomavirus; LVSI, lymphovascular space invasion.

pattern classifications were investigated in univariate models, and all were variably significant factors for disease recurrence and DSS. In the multivariate model and after adjustment for patient age and FIGO stage, only the 2-tier/binary Silva pattern of invasion (including LVSI status) remained prognostically significant for both disease recurrence and DSS. The significant association between LVSI and outcome is of interest; however, it is important to note that the Silva pattern of invasion is partly defined by the presence or absence of LVSI and it is possible that the strong prognostic association of the Silva classification is due to this particular feature rather than other morphologic features. It is also possible that LVSI and the pattern of invasion act in a synergistic manner; for example, it has been reported that the presence or absence of LVSI has a modifying effect on the behavior of pattern C tumors.[27] It is worth noting that, although rare, recurrence (n = 7, 3.5%) and death due to disease (n = 1, 0.5%) were seen in patients with pattern A tumors and although this finding calls into question whether these tumors were classified correctly, it has been recently shown that pattern A tumors can rarely recur, sometimes many years after initial diagnosis.[28]

This study has a number of strengths including most importantly 1) multi-institutional data derived from the real-world practice of a large number of pathologists who participated in mandatory online training for histologic and Silva

TABLE 3. Locations of Tumor Recurrence, Organized by Silva Pattern of Invasion

		Location of recurrence				
Pattern	**Stage**	**Local/pelvic (non-nodal) only**	**Distant only**	**Nodal (local or distant) only**	**Combination**	**Unknown/not specified**
A	IA2	1	—	—	—	—
	IB1	1	—	1	1	—
	IB2	2	—	—	—	1*
B (−LVSI)	IA2	1	—	—	—	—
	IB1	4	1*	1*	2	—
	IB2	1 + 1*	—	—	—	1*
B (+LVSI)	IA2	—	—	—	—	—
	IB1	2	1*	—	—	—
	IB2	1 + 1*	—	—	—	1
C	IA2	—	—	—	1*	—
	IB1	14 + 3*	2 + 1*	1	—	1*
	IB2	9	3	1	5 + 1*	1*
	IB3	2 + 2*	1	—	—	—

*Patients who died of endocervical adenocarcinoma.
LVSI, lymphovascular space invasion.

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TABLE 4. Univariate (unadjusted) Competing Risk Model Investigating Factors (Including the Silva Pattern of Invasion) Associated With Disease Recurrence and DSS for the Cohort (n = 792)

	Disease recurrence			DSS		
Characteristic	**sHR**	**95% CI**	***P***	**sHR**	**95% CI**	***P***
Age (yr)						
< 50	0.71	0.52–0.96	0.026	0.84	0.36–1.98	0.694
≥ 50	1.0	—	—	1.0	—	—
FIGO stage						
Stage IA2	0.28	0.87–0.94	0.039	0.49	0.10–2.46	0.386
Stage IB1	1.0	—	—	1.0	—	—
Stage IB2	1.31	0.89–1.91	0.167	1.74	0.88–3.41	0.109
Stage IB3	1.02	0.32–3.22	0.977	1.80	0.23–14.31	0.577
Lymphovascular invasion status						
Absent	1.0	—	—	1.0	—	—
Present	2.42	1.74–3.37	0.000	5.16	2.23–11.94	0.000
3-tier Silva pattern of invasion						
Pattern A	0.24	0.09–0.62	0.003	0.14	0.39–0.51	0.003
Pattern B	0.49	0.27–0.86	0.013	0.56	0.59–1.71	0.371
Pattern C	1.0	—	—	1.0	—	—
4-tier Silva pattern of invasion						
Pattern A	0.24	0.09–0.62	0.003	0.14	0.39–0.51	0.003
Pattern B (−LVSI)	0.44	0.23–0.84	0.014	0.32	0.59–1.71	0.181
Pattern B (+LVSI)	0.63	0.28–1.44	0.278	1.18	0.30–4.60	0.813
Pattern C	1.0	—	—	1.0	—	—
2-tier Silva pattern of invasion						
Pattern A and pattern B (−LVSI)	0.36	0.22–0.58	0.000	0.22	0.07–0.63	0.005
Pattern B (+LVSI) and pattern C	1.0	—	—	1.0	—	—

DSS, disease-specific survival; FIGO, International Federation of Gynecology and Obstetrics; LVSI, lymphovascular space invasion; sHR, subdistribution hazard ratio.

TABLE 5. Multivariate (adjusted) Competing Risk Model Investigating Factors (Including the 3-tier Silva Pattern of Invasion) Associated With Disease Recurrence and DSS for the Cohort (n = 792)

	Adjusted model					
	Disease recurrence			DSS		
Characteristic	**sHR**	**95% CI**	***P***	**sHR**	**95% CI**	***P***
Age (yr)						
< 50	0.75	0.57–0.98	0.038	0.82	0.35–2.05	0.719
≥ 50	1.0	—	—	1.0	—	—
FIGO stage						
Stage IA2	0.34	0.11–0.99	0.048	0.56	0.10–3.15	0.672
Stage IB1	1.0	—	—	1.0	—	—
Stage IB2	1.08	0.74–1.58	0.683	1.29	0.65–2.59	0.470
Stage IB3	0.73	0.22–2.42	0.605	0.95	0.12–7.43	0.965
Lymphovascular invasion status						
Absent	1.0	—	—	1.0	—	—
Present	1.83	1.24–2.72	0.003	3.91	1.52–10.08	0.005
Silva pattern of invasion						
Pattern A	0.36	0.16–0.82	0.016	0.32	0.13–0.79	0.013
Pattern B	0.55	0.31–0.98	0.042	0.65	0.16–2.57	0.540
Pattern C	1.0	—	—	1.0	—	—

DSS, disease-specific survival; FIGO, International Federation of Gynecology and Obstetrics; sHR, subdistribution hazard ratio.

TABLE 6. Multivariate (adjusted) Competing Risk Model Investigating Factors (Including the 4-tier Silva Pattern of Invasion) Associated With Disease Recurrence and DSS for the Cohort (n = 792)

	Adjusted model					
	Disease recurrence			DSS		
Characteristic	**sHR**	**95% CI**	***P***	**sHR**	**95% CI**	***P***
Age (yr)						
< 50	0.72	0.54–0.95	0.021	0.79	0.34–1.86	0.593
≥ 50	1.0	—	—	1.0	—	—
FIGO stage						
Stage IA2	0.34	0.12–1.00	0.050	0.59	0.11–3.04	0.530
Stage IB1	1.0	—	—	1.0	—	—
Stage IB2	1.15	0.79–1.67	0.459	1.42	0.71–2.86	0.320
Stage IB3	0.83	0.25–2.81	0.765	1.32	0.16–10.86	0.793
Silva pattern of invasion						
Pattern A	0.28	0.13–0.62	0.002	0.17	0.06–0.45	0.000
Pattern B (−LVSI)	0.47	0.23–0.96	0.038	0.35	0.06–2.09	0.249
Pattern B (+LVSI)	0.70	0.30–1.64	0.419	1.29	0.30–5.57	0.729
Pattern C	1.0	—	—	1.0	—	—

DSS, disease-specific survival; FIGO, International Federation of Gynecology and Obstetrics; LVSI, lymphovascular space invasion; sHR, subdistribution hazard ratio.

pattern classification systems, 2) histologic rereview of all cases by contributing pathologists to ensure accuracy of reported parameters, and 3) utilization of a robust statistical methodology to ensure reliability of the results. It is also worth noting that many of the important clinicopathological characteristics of the cohort (eg, distribution of patient age, tumor type, pattern of invasion, and stage) and how they are proportioned is what would be expected in the population and generally matches previously reported smaller cohorts. Despite this and the fact that data were contributed from a number of institutions from different areas of the world, overall, data originated almost exclusively from highly developed countries and given possible geographic bias, generalization of the results to areas that are not specifically represented cannot be automatically assumed.

The main limitations are the retrospective design, nonconsecutive nature of the included cases, and wide range of follow-up periods. It is possible that a selection bias or exposure to confounding variables, such as neoadjuvant and adjuvant chemotherapy (outside the scope of this study), could also have influenced the outcomes of the study. It should be noted that although the mandatory online training was comprehensive, it did not specifically teach or train on the assessment of LVSI. The reproducibility of LVSI in the assessment of endometrial cancers is known to be high[29] and, presumably, this high level of reproducibility extends to the assessment of EACs; however, this has not been specifically studied and the influence of LVSI on the results of this study may possibly be altered based on LVSI grading (i.e. [semi]quantification of the number of spaces involved) in these tumors. The excellent outcomes observed, with very few deaths due to disease (< 3%) and a low relative proportion of recurrences overall (< 10%), confirm the successful management in this large series of EACs but, it is also a limitation of this study, as it reduces statistical power due to the small number of events.

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TABLE 7. Multivariate (adjusted) Competing Risk Model Investigating Factors (Including the Silva Pattern of Invasion as a Binary Classification System) Associated With Disease Recurrence and DSS for the Cohort (n = 792)

	Adjusted model					
	Disease recurrence			DSS		
Characteristic	sHR	95% CI	*P*	sHR	95% CI	*P*
Age (yr)						
< 50	0.70	0.52–0.94	0.017	0.82	0.35–1.94	0.657
≥ 50	1.0	—	—	1.0	—	—
FIGO stage						
Stage IA2	0.33	0.10–1.02	0.055	0.58	0.11–3.01	0.513
Stage IB1	1.0	—	—	1.0	—	—
Stage IB2	1.17	0.79–1.73	0.423	1.43	0.70–2.92	0.332
Stage IB3	0.84	0.25–2.80	0.780	1.31	0.16–10.95	0.801
Silva pattern of invasion						
Pattern A and pattern B (−LVSI)	0.40	0.24–0.65	0.000	0.25	0.08–0.77	0.016
Pattern B (+LVSI) and pattern C	1.0	—	—	1.0	—	—

DSS, disease-specific survival; FIGO, International Federation of Gynecology and Obstetrics; LVSI, lymphovascular space invasion; sHR, subdistribution hazard ratio.

The latter also limits our ability to use this data set to investigate other important clinical management questions (eg, pathologic factors that strongly point towards lymph node assessment not being required or indicate an exceptionally high risk of local or nodal recurrence).

The power of the combined findings of the binary Silva system and the lack of significance of stage I substaging in this study call into question the significance of early-stage tumor substaging in EACs and specifically highlights the power of LVSI as a prognostic factor in predicting patient outcome. These findings indicate a clear need for prospective studies to further assess the prognostic significance of FIGO I substaging and the binary Silva pattern of invasion classification (which includes LVSI status) to assist in the refinement of the treatment recommendations for this group of tumors.[30] To bridge the pathologic adoption of the pattern-based classification system with its incorporation into clinical management algorithms, further investigation where the predictive power and clinical safety profile of this framework are studied in the context of clinical trials is necessary. These next steps will undoubtedly provide invaluable information that will aid in establishing the (binary) pattern-based classification system as a clinically relevant tool. Pathologists who examine specimens from patients with these tumors will play a critical role in its integration into routine decision-making algorithms for the personalized and refined treatment of HPV-associated EAC.

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