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Original contribution

Study of the revisited, revised, and expanded Silva pattern system for Chinese endocervical adenocarcinoma patients☆,☆☆,★

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Summary As a new pattern-based classification, the Silva pattern system has been recently developed to evaluate invasive lymph node metastasis and the prognosis of endocervical adenocarcinoma (EAC). Therefore, our study was conducted to explore the reproducibility and prognostic significance of this system in a multi-institutional Chinese cohort, with the goal of revising and expanding its application. The clinicopathological data of 191 EAC patients from 3 medical centers were examined in a retrospective manner. The Silva pattern system demonstrated great prognostic value, significance in guiding treatment selection, and acceptable reproducibility in 191 patients that included additional histologic variants and 124 usual-type EAC patients. Collectively, compared with usual-type EAC, the whole cohort demonstrated similar statistical significance for relevant clinicopathological parameters, such as International Federation of Gynecology and Obstetrics stage (R = 0.612 versus R = 0.600), tumor thickness (P < .0001 versus P < .0001), lymphovascular invasion (P < .0001 versus P < .0001), lymph node metastasis (P = .033 versus P = .018), perineural invasion (P = .003 versus P = .001), and recurrence-free survival (P = .047 versus P = .020). Moreover, perineural invasion was significantly correlated (P = .001) with the Silva pattern system and appeared in most Silva C tumors. In conclusion, the Silva pattern system is consistent with the biological behavior of EAC and has acceptable reproducibility. Compared with International Federation of Gynecology and Obstetrics stage, it can predict patient prognosis before surgery. We suggest revising the Silva C criteria by adding perineural invasion as a factor and propose expanding the Silva pattern system to include more histologic variants. It seems that the Silva pattern system can be applied in routine clinical practice to guide EAC therapeutic strategies in the near future.

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1. Introduction

As the fourth most common malignant tumor affecting women, cervical carcinoma has attracted great attention worldwide. Most endocervical adenocarcinomas (EACs) are related to high-risk, human papillomavirus infection, especially the human papillomavirus 18 genotype. With the adoption of effective screening measures for cervical carcinoma, the incidence of cervical squamous cell carcinoma has dropped considerably in recent decades. Conversely, both the proportion and the quantity of EACs are gradually increasing. At present, there are some controversies and dilemmas regarding the diagnosis and treatment of EACs.

The maximum diameter of EAC, which is regarded as one of the important risk factors according to International Federation of Gynecology and Obstetrics (FIGO) staging, is usually difficult to measure owing to their diffusely infiltrating growth patterns, which can lead to a barrel-shaped cervix. According to the 2014 version of the World Health Organization classification, most EACs are classified as usual type, so that the prognostic value of particular histologic tumor types is limited. Histologic grading of EACs shows slight significance in predicting prognosis. On one hand, most EACs belong to well-moderate differentiation according to current grading systems. However, some extremely well-differentiated EACs, such as minimal deviation adenocarcinoma, are highly aggressive. A clear distinction of invasive EAC from adenocarcinoma in situ (AIS) is not possible in up to 20% of cervical glandular lesions [1]. A triage system for EACs has not been well developed. According to the National Comprehensive Cancer Network guidelines, tumors with greater than 3 mm of invasion undergo hysterectomy and lymphadenectomy, even with adjuvant therapy. These aggressive treatments can produce significant morbidity, such as dysuresia and lymphedema.

In recent years, a new pattern-based histopathologic classification for invasive EAC, named the Silva pattern system, has been proposed [2-4]. By evaluating the growth pattern of tumor cells, pathologists can estimate tumor biological behavior. Compared with conventional pathologic grading systems, this novel classifier is aimed at better predicting nodal metastasis and prognosis, which can refine therapeutic strategies [2-4]. However, some refinement of the Silva pattern system is necessary. Because analysis of the Silva pattern system has only been reported with limited cohorts [1,3], both the reproducibility and the prognostic value of this methodology need to be confirmed and validated. In addition, only usual-type EAC has been assessed using the Silva pattern system, but other special types of EAC account for approximately 10% of total incidence of this malignancy, with some mixed adenocarcinomas being occasionally detected. It is unclear whether other potential prognosticators, such as perineural invasion (PNI), should be added to better define Silva C tumors.

In this study, we aimed to investigate and expand the applicability and prognostic significance of the Silva pattern system in nonusual histologic tumor types of EAC in Chinese patients. In addition, we also aimed to improve risk assessment by incorporating additional clinicopathological information into the Silva pattern system.

2. Materials and methods

All relevant clinical data were used in a retrospective analysis of routine follow-up data, and all patient data were anonymized.

Our selection criteria included the following: (1) tumors diagnosed as AIS or invasive EAC; (2) tumors resected by the cone/loop electrosurgical excision procedure, trachelectomy, and/or hysterectomy, ensuring EAC tumors were available for microscopic examination; and (3) lymphadenectomy or clinical/radiologic evidence of metastatic nodal disease.

Table 1 The Silva pattern system criteria

Pattern	Criteria
Pattern A	1. Well-demarcated glands with rounded contours, frequently forming groups 2. No single cells or cell detachment, lack of solid growth 3. Complex intraglandular growth acceptable (ie, cribriform, papillae) 4. No destructive stromal invasion 5. No LVI
Pattern B	1. Individual or small groups of tumor cells, separated from the rounded gland, foci may be single, multiple, or linear at base of tumor 2. Lack of solid growth 3. Localized destructive stromal invasion arising from pattern A glands, or focally desmoplastic or inflamed stroma 4. LVI +/−
Pattern C	1. Glands often angulated or with a canalicular pattern, with interspersed open glands 2. Confluent growth filling a 4× field (5 mm) 3. Solid, poorly differentiated component 4. Diffuse destructive stromal invasion, characterized by diffusely infiltrative glands, with associated extensive desmoplastic response 5. LVI +/−

The data of 191 patients were collected from 3 Chinese medical centers, including Peking University Third Hospital, Dalian Obstetrics and Gynecology Hospital, and China-Japan Friendship Hospital. Ten patients had been previously misdiagnosed with and treated for AIS, whereas the remaining patients were diagnosed with and treated for invasive EACs. Three senior pathologists reviewed all slides and stratified cases into pattern A, B, or C by consensus according to the Silva pattern system criteria (Table 1) [2,4]. There were 6 histologic tumor types found in our study cohort (Table 2). All adenosquamous carcinomas (ASCs) were classified according to the growth pattern of adenocarcinoma components.

Pathologic data analyzed included the following: tumor thickness, lymphovascular invasion (LVI), lymph node (LN) metastasis, and PNI. Clinical data analyzed included the following: age, FIGO stage, adjuvant therapy, and receiving chemotherapy and/or radiotherapy. The follow-up data collected included the following: recurrence, date of recurrence, mortality, date of death, and survival period.

The χ^2 test was performed to investigate the statistical correlation between Silva pattern system and various clinicopathological parameters, including FIGO stage, tumor thickness, LVI, LN metastasis, PNI, recurrence, and mortality. Overall survival (OS) and recurrence-free survival (RFS) were assessed using the Kaplan-Meier method. The end point of the OS analysis was the duration to date of death, and RFS was characterized as the length of time until disease progression. All statistical analyses were performed using SPSS version 20.0 (IBM, Armonk, NY), including all descriptive statistics. $P < .05$ was considered statistically significant.

3. Results

The clinicopathological characteristics of all 191 EAC patients are shown in Table 2. Patient age of the cohort ranged from 27 to 85 years (median, 45 years; mean, 45 years). Approximately 1 (22.5%) of 5 of patients received cervical conization, with the remaining patients receiving a hysterectomy. LVI, LN metastasis, and PNI were discovered in 66 (34.6%), 23 (16.7%), and 20 (10.5%) patients, respectively. Thirty-nine patients were lost to follow-up.

Nearly 1 (24.1%) of 4 of patients were classified as having pattern A tumors, and all of these tumor types were FIGO stage I (IA1, 33; IB1, 13). Among these patients, 10 were previously misdiagnosed with AIS (Table 3, Fig. 1A). Tumor thickness ranged from 1.00 to 10.00 mm (mean, 2.95 mm). Neither LVI nor PNI was detected in this group of patients. LNs were resected from 16 patients (total LNs, 361; range, 7-40 resected LNs per patient; mean, 22 LNs per patient); all of these patients were negative for metastatic carcinoma. Follow-up was available for 45 patients (range, 5-131 months; mean, 43.0 months; median, 37 months). All patients with pattern A tumors were alive at time of follow-up and had no evidence of recurrence.

Table 2 Clinicopathological characteristics of the 191 EAC patients in this study

Parameter	n	%
Histologic type		
Usual	124	64.9
Villoglandular	22	11.5
Mucinous	15	7.9
Endometrioid	3	1.6
Clear cell	2	1.0
Adenosquamous	26 [a]	13.6
FIGO stage		
IA	44	23.0
IB	123	64.4
IIA	17	8.9
IIB	6	3.1
III	1	0.5
Surgery		
Cervical conization	43	22.5
Hysterectomy	148	77.5
Lymphadenectomy		
Yes	138	72.3
No	53	27.7
Chemotherapy		
Yes	73	38.2
No	118	61.8
Radiotherapy		
Yes	49	25.7
No	142	74.3
LVI		
Present	66	34.6
Absent	125	65.4
LN metastasis [b]		
Present	23	16.7
Absent	115	83.3
PNI		
Present	20	10.5
Absent	171	89.5
Recurrence [c]		
Present	5	3.3
Absent	147	96.7
Death [d]		
Present	2	1.3
Absent	148	98.7

Abbreviation: NEC, neuroendocrine carcinoma.
[a] One case was villoglandular carcinoma admixed with squamous carcinoma.
[b] No lymphadenectomy in 53 cases.
[c] Thirty-nine cases were lost to follow-up.
[d] Forty-one cases were unknown of newest survival condition.

Forty-one cases (21.5%) were classified as pattern B tumors. All cases were FIGO stage I, including 7 IA1, 2 IA2, and 32 IB1 (Table 3, Fig. 1B). Tumor thickness ranged from 0.5 to 10.0 mm (mean, 4.50 mm). LVI was detected in 6 patients (14.6%), and PNI was detected in 2 patients (4.9%). LNs were resected from 30 patients (total LNs, 638; range, 10-44 resected LNs per patient; mean, 21 LNs per

Table 3 Clinicopathological parameters based on the Silva pattern system and statistical correlations in the 191 EAC patients

Parameter	Silva system			P
	A (n = 46; 24.1%)	B (n = 41; 21.5%)	C (n = 104; 54.5%)	
FIGO stage				<.0001
IA	33	9	2	
IB	13	32	78	
IIA	0	0	17	
IIB	0	0	6	
III	0	0	1	
IV	0	0	0	
Mean depth of tumor (mm)	2.95	4.50	10.66	<.0001
LVI				<.0001
Present	0	6	60	
Absent	46	35	44	
LN metastasis [a]				
Present	0	2	21	.018
Absent	16	28	71	
PNI				
Present	0	2	18	.001
Absent	46	39	86	
Recurrence [b]				
Present	0	0	5	.086
Absent	45	37	65	
Death [c]				
Present	0	0	2	.501
Absent	45	37	66	

[a] No lymphadenectomy in 53 cases.
[b] Thirty-nine cases were lost to follow-up.
[c] Forty-one cases were unknown of newest survival condition.

patient). Only 2 patients had positive LNs, and both also had LVI. Follow-up was available for 37 patients (range, 7-104 months; mean, 35.1 months; median, 23.5 months). All patients were alive at the last follow-up, with no evidence of recurrence.

The remaining 104 patients (54.5%) had tumors with morphologic features of pattern C. Most of these patients (76.9%) were diagnosed with FIGO stage I (IA1, 2; IB1, 68; IB2, 10); 23 patients (22.1%) had FIGO stage II tumors (IIA, 17; IIB, 6), and 1 patient had a stage III tumor (Table 3, Fig. 1C). Tumor thickness ranged from 2.00 to 26.00 mm (mean, 10.66 mm). LVI was present in 60 patients (57.7%), and PNI was detected in 18 patients (17.3%). LNs were resected in 92 patients (total LNs, 2263; range, 5-50 resected LNs per patient; mean, 24.6 LNs per patient). LN metastasis was discovered in 21 patients (22.8%). Follow-up was available for 70 patients (range, 4-127 months; mean, 37.0 months; median, 30 months). Recurrence was detected in 5 patients (7.1%); 2 patients (2.9%) had recurrence in the pelvic region and 3 (4.3%) had distant recurrence. At the last follow-up, 2 patients had died of the disease between 34 and 93 months.

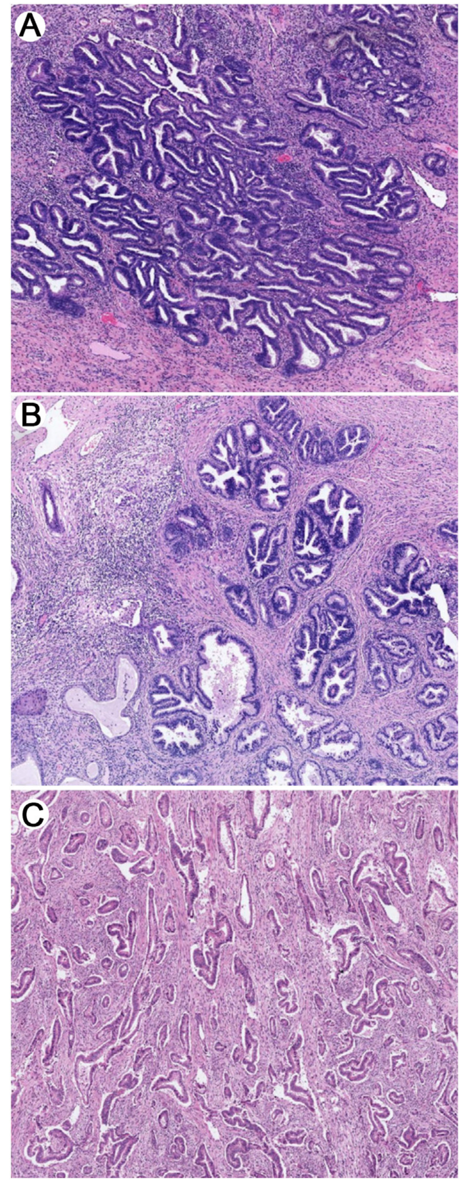


Fig. 1 A, Well-demarcated glands forming groups, corresponding to pattern A tumor. B, Glands with irregular contours in a localized desmoplastic stroma arising from pattern A type glands, corresponding to pattern B tumor. C, Diffuse angulated or canalicular glands of pattern C tumor. A-C, Hematoxylin and eosin staining, original magnification ×40.

Of the whole cohort of 191 EAC patients, 124 usual-type EACs were analyzed independently using the above criteria (Table 4). The Silva pattern system was closely correlated with FIGO stage in both the usual-type subgroup (R = 0.612, $P < .0001$), as well as the whole cohort (R = 0.600, $P < .0001$). These 2 groups demonstrated significant differences in tumor thickness ($P < .0001$ versus $P < .0001$) and LVI ($P < .0001$ versus $P < .0001$). Interestingly, the whole cohort showed a more significant difference than did the usual-type subgroup for LN metastasis (P = .018 versus

Table 4 Correlation between clinicopathological parameters of 124 usual-type EAC patients and Silva pattern system

Parameter	Silva system			*P*
	A (n = 36; 29.0%)	B (n = 20; 16.1%)	C (n = 68; 54.8%)	
FIGO stage				<.0001
IA	26	8	1	
IB	10	12	51	
IIA	0	0	10	
IIB	0	0	5	
III	0	0	1	
IV	0	0	0	
Mean depth of tumor (mm)	2.96	4.40	10.52	<.0001
LVI				
Present	0	2	43	<.0001
Absent	36	18	25	
LN metastasis [a]				
Present	0	0	15	.033
Absent	11	11	44	
PNI				
Present	0	0	12	.003
Absent	36	20	56	
Recurrence [b]				
Present	0	0	5	.074
Absent	35	18	40	
Death [c]				
Present	0	0	1	1.000
Absent	35	18	42	

[a] Forty-three cases did not do lymphadenectomy.
[b] Twenty-six cases were lost to follow-up.
[c] Twenty-eight cases were unknown of newest survival condition.

P = .033), PNI (*P* = .001 versus *P* = .003), and RFS (*P* = .020 versus *P* = .047). However, unlike differences noted in FIGO stage (*P* = .001), neither the whole cohort nor the usual-type subgroup showed a significant difference in OS (*P* = .185 versus *P* = .646; Fig. 2).

Furthermore, a similar analysis was performed for 67 nonusual type tumors, which showed that a significant difference of the Silva pattern system was shown in FIGO stage (*P* < .0001), tumor depth (*P* < .0001), and LVI (*P* = .004). Details are shown in Table 5.

In addition, a subgroup of 22 villoglandular adenocarcinomas (VGAs) were stratified into 3 patterns (pattern A, 5; pattern B, 10; pattern C, 7) according to the Silva pattern system. Most (80%) pattern A cases were FIGO stage IA, and most (94.1%) pattern B and C patients were FIGO stage IB. All patients who had LVI and/or LN metastasis had tumors classified as pattern B or C. Statistical results showed that pattern C VGAs were significantly thicker (*P* = .002) and had higher FIGO stage (*P* = .023) than pattern A and B VGAs.

We also stratified 26 ASCs according to the Silva pattern system. Silva grades were significantly correlated with tumor thickness in this subgroup (*P* = .011).

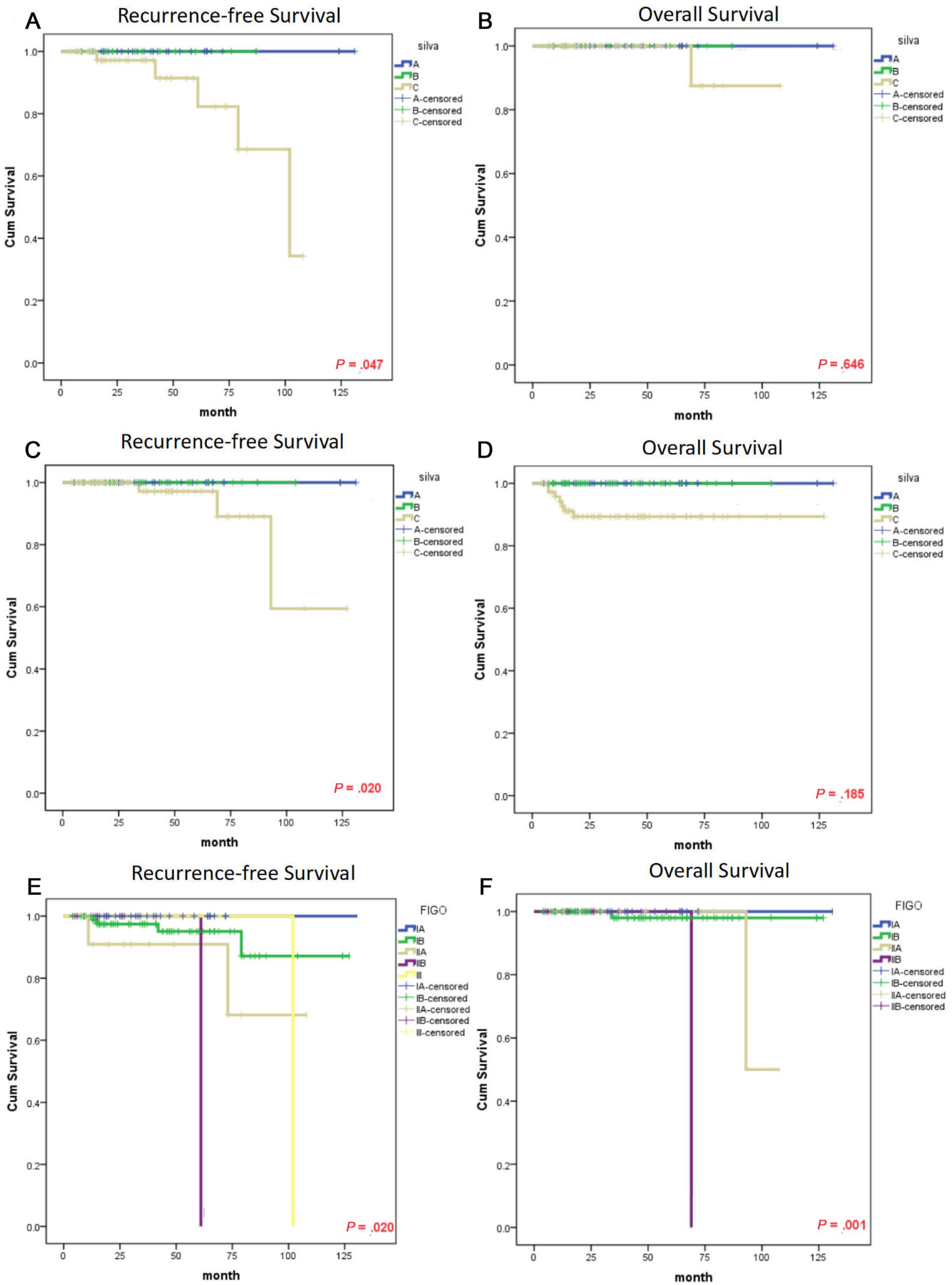
4. Discussion

In current practice, EACs are treated and managed in a similar manner to that of cervical squamous cell carcinoma, according to FIGO stage and National Comprehensive Cancer Network guidelines. However, this management tends to be nonspecific and may lead to overtreatment. Therefore, it is advisable to refine the risk assessment associated with EAC [1]. Based on recent progress in modern pathology, the Silva pattern system has been developed to provide unique information for the treatment of EAC.

Our study demonstrated a similar distribution (Silva A, 24.1%; Silva B, 21.5%; and Silva C, 54.5%) to that shown in published data [2,4], providing evidence for the reproducibility of the Silva pattern system. According to the present study, the Silva pattern system was concordant with FIGO staging; all Silva A and B EACs were stage I, whereas nearly 25.0% of Silva C tumors were stages II to IV. Although the proportion of the Silva C subgroup was similar to that of published data, Silva C patients in our cohort demonstrated higher FIGO stages than did patients from developed countries [5]. As a vast country with large population, the medical resource allocation is unbalanced in China, and health care information should be disseminated to promote cervical cancer screening.

Consistent with published data [2,4], Silva grading in our study was correlated with tumor thickness, LVI, LN metastasis, recurrence rate, and RFS. According to modern oncology models, pattern A tumors represent tumor cells with expansive growth patterns [6]. These tumor cells have strong proliferation tendencies and prominent cell-cell junctions, but because of a lack of ability for active migration, the surrounding tissues cannot confine these proliferating tumor cells, resulting in the tumor cells invading the stroma through increasing in volume rather than active migration. Therefore, in theory, destructive stromal invasion, LVI, and LN metastasis should not be found in this category of tumor, which should result in these patients having excellent prognosis.

When cell-cell junctions are absent, tumor cells possess the ability to migrate individually. Distinct from pattern A tumors, an epithelial-mesenchymal transition can be found in pattern B tumors, although it is often very focal. These tumor cells own focalized proteases on the cell surface and cell-matrix adhesions, resulting in these cells possessing the ability to change their bodies into spindle morphologies when invasive migration occurs [6]. If there are low adhesion forces and high contractility present within the tumor cells, their bodies are typically spherically shaped like signet-ring cells. These cells can adapt their shape to tissue gaps without destroying the surrounding matrix. This special migration is called amoeboid migration [6]. Although most pattern B tumors are similar to pattern A tumors in terms of growth, these tumor cells are focally invasive. Moreover, individual cells from these tumors can be observed as separate from the main body of the tumor, with a localized desmoplastic stroma, and there is a small possibility of LVI and LN metastasis.


A
Recurrence-free Survival
Cum Survival
month
silva
A
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A
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C
A-censored
B-censored
C-censored
P = .646
C
Recurrence-free Survival
Cum Survival
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Overall Survival
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Overall Survival
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IIA-censored
IIB-censored
P = .001

Table 5 Correlation between clinicopathological parameters of 67 non–usual-type EAC patients and Silva pattern system

Parameter	Silva system			*P*
	A (n = 10; 14.9%)	B (n = 21; 31.3%)	C (n = 36; 53.7%)	
FIGO stage				<.0001
IA	7	1	1	
IB	3	20	27	
IIA	0	0	7	
IIB	0	0	1	
III	0	0	0	
IV	0	0	0	
Mean depth of tumor (mm)	2.95	4.73	10.03	<.0001
LVI				
Present	0	4	17	.004
Absent	10	17	19	
LN metastasis [a]				
Present	0	2	6	.618
Absent	5	17	27	
PNI				
Present	0	2	6	.465
Absent	10	19	30	
Recurrence [b]				
Present	0	0	0	.279
Absent	10	19	25	
Death [c]				.667
Present	0	0	1	
Absent	10	19	24	

[a] Ten cases did not do lymphadenectomy.
[b] Thirteen cases were lost to follow-up.
[c] Thirteen cases were unknown of newest survival condition.

By infiltrating via multicellular collective migration, pattern C tumors are regarded as the most aggressive subtype of tumor in the Silva system. Most of the tumor cells lose cell-cell adhesion, with the exception of cells in the middle of the tumor, so that they can migrate simultaneously as a group. Pattern C tumors can adopt different morphologies, and different shapes can be observed, such as angulated or open glands and even solid components [6]. In the process of invasion, diffuse destructive stroma is shaped by the participation of many stromal cells. Contrary to a former view [7], stromal cells can help create the tumor microenvironment. For example, tumor-related fibroblasts can produce collagen fibers to remodel tissue structure, and they can release cytokines and growth factors to aid tumor cell invasion. Tumor-infiltrating lymphocytes release some signaling molecules [8], including tumor growth factor, epidermal growth factor, and chemokines, which serve as effectors of tumor-promoting actions. These cells can produce matrix-degrading enzymes, such as MMP-9, to aid tumor migration. The cells can also mislead the immune system to recognize tumor cells as benign cells. Therefore, pattern C tumors can invade surrounding tissues without resistance, which explains the recommendation that these tumors should be treated with aggressive surgery.

Ten of 36 patients with pattern A tumors were previously misdiagnosed with AIS, reflecting the difficulty in discriminating AIS and superficial invasive EAC. Distinctions between AIS and invasive EAC show slight agreement in daily practice, and this has been indicated in a previous study [1]. In conventional nomenclature, AIS is defined as prominent cellular atypia and active mitotic figures with intact lobular structure. In contrast, invasive EAC is referred to as having greater structural atypia, such as glandular complexity, like papillary growth, cribriform, and solid glands, or well-demarcated glands forming groups with round contours that lose the normal lobule structure. However, the above criteria are somewhat subjective, especially in superficial invasive tumors that lack destructive stroma. Therefore, because of a similar and excellent prognosis [1], AIS and Silva A EAC are proposed to be categorized into the "EAC with nondestructive growth" entity [2,4]. Recent genomic data provide strong support for this proposal. Genetically, pattern A tumors seem to be conspicuously different from pattern B and C tumors [9]. Compared with Silva A, Silva B tumors tend to have *KRAS* mutations [9], which can increase the likelihood of recurrence [10]. *PIK3CA* mutations are associated with a higher rate of distant metastases [11] and were found to be more common in Silva C tumors [9].

As a notoriously adverse prognostic factor for EAC [12], PNI (Fig. 3) has not been investigated by prior Silva-related studies. In our study, PNI was significantly correlated (P = .001) with Silva grade, with almost all PNI appearing in Silva C tumors. Physically, epineurial, perineurial, and endoneurial spaces of the neuronal sheath are loose connective tissues. Once tumor cells arrive at these low-resistance channels, they can rapidly migrate along the "highway of migration" [13]. Biologically, nerve cells can release many cytokines, such as neural cell adhesion molecules and neural growth factors, which can promote tumor cells accumulation near nerve cells

Fig. 2 Kaplan-Meier curves. A, RFS curves of 124 usual-type endocervical carcinoma patients according to the Silva system. The survival periods of C-type patients were significantly shorter than A- and B-type patients. B, OS curves of 124 usual-type EAC patients according to the Silva system. There was no significant difference among the 3 groups. C, RFS curves of 191 EAC patients according to the Silva system. The survival periods of C-type patients were significantly shorter than those of A- and B-type patients. D, OS curves of 191 EAC patients according to the Silva system. There was no significant difference among the 3 groups. E, RFS curves of 191 EAC patients according to FIGO stage. There were significant differences among the patient groups. F, OS curves of 191 EAC patients according to FIGO stage. There were significant differences among the patient groups.

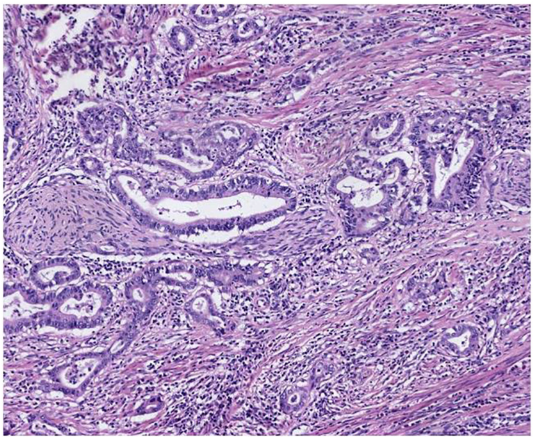

Fig. 3 Pattern C tumor with PNI. Hematoxylin and eosin staining, original magnification ×100.

and result in nerve invasion [13,14]. PNI is thus highly related to tumor diameter, the depth of stromal invasion, parametrial infiltration, positive margins, LVI, and LN metastasis [13,15]. Accordingly, we suggest that PNI be added to revised criteria for Silva C pattern tumors, which may improve the prediction of adverse prognoses.

In addition to usual-type EAC, we evaluated non–usual-type subgroups, a category that included some special histologic variants; this analysis demonstrated significant difference in FIGO stage, tumor depth, and LVI. Collectively, our complete patient cohort demonstrated similar statistical significance for all relevant clinicopathological parameters.

Although VGA was considered by the World Health Organization classification as an entity with excellent outcome, some VGA patients develop LN metastasis and eventually die of this disease [16-18]. In our VGA subgroup of 22 patients, those with LN metastasis and a poor prognosis tended to exhibit focally or diffuse invasive morphologies, and/or LVI in their deeper components. We therefore suggest that VGA, which was named for its distinct exophytic, villous-papillary growth pattern, should not be regarded as an independent entity. In particular, it should not be used for biopsy diagnosis, which could result in undertreatment by misinterpretation. The final surgical strategy must be decided from the deeper components of the VGA tumor, which should be evaluated by the Silva pattern system using cervical conization specimens.

Mucinous EAC was also assessed by the Silva pattern system in this study. Although most of these tumors, especially minimal deviation adenocarcinoma, were well differentiated with minimal cell atypia, they are characterized by angulated, irregular, or fused glands, which represent multicellular collective migration and are usually associated with desmoplastic or destructive stroma. Accordingly, most mucinous EACs were classified as pattern C tumors, which is in concordance with their notoriously adverse prognosis [19] and poor 5-year disease-free survival.

The outcome of cervical ASC has been shown to be worse than that of cervical squamous carcinoma but similar to that of EACs [20]. In addition, it is believed that adenocarcinoma components have a larger impact on patient survival [20]. Within the ASC subgroup, Silva grades were significantly correlated with tumor thickness and tended to be positively associated with LVI, but the difference did not reach statistical significance, which could be attributed to the small number of patients. Although further elucidation is required, the evaluation of ASC by the Silva pattern system shows promise.

By revisiting the Silva pattern system in this Chinese cohort, our study confirmed the satisfactory prognostic value, significance for guiding treatment decisions, and acceptable reproducibility of this system [3,21,22]. In addition, we suggest revising the Silva C criteria by adding PNI as an important factor. Moreover, we propose expanding the Silva pattern system to include more histologic variants. In conclusion, although some aspects of this system will need to be investigated further, it seems that the Silva pattern system can be applied in routine clinical practice to guide defined therapeutic strategies for EAC in the near future.

References

[1] Parra-Herran C, Taljaard M, Djordjevic B, et al. Pattern-based classification of invasive endocervical adenocarcinoma, depth of invasion measurement and distinction from adenocarcinoma in situ: interobserver variation among gynecologic pathologists. Mod Pathol 2016;29:879-92.

[2] Roma AA, Mistretta T, Diaz De Vivar A, et al. New pattern-based personalized risk stratification system for endocervical adenocarcinoma with important clinical implications and surgical outcome. Gynecol Oncol 2016;141:36-42.

[3] Rutgers JK, Roma AA, Park KJ, et al. Pattern classification of endocervical adenocarcinoma: reproducibility and review of criteria. Mod Pathol 2016;29:1083-94.

[4] Roma AA, Vivar ADD, Park KJ, et al. Invasive endocervical adenocarcinoma: a new pattern-based classification system with important clinical significance. Am J Surg Pathol 2015;39:667-72.

[5] Djordjevic B, Parra-Herran C. Application of a pattern-based classification system for invasive endocervical adenocarcinoma in cervical biopsy, cone and loop electrosurgical excision (LEEP) material. Int J Gynecol Pathol 2016;35:456-66.

[6] Friedl P, Alexander S. Cancer invasion and the microenvironment: plasticity and reciprocity. Cell 2011;147:992-1009.

[7] Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. Nature 2008;454:436-44.

[8] Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011;144:646-74.

[9] 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;30:1633-41.

[10] Xiang L, Li J, Jiang W, et al. Comprehensive analysis of targetable oncogenic mutations in chinese cervical cancers. Oncotarget 2014;6:4968-75.

[11] Xiang L, Jiang W, Li J, et al. PIK3CA mutation analysis in Chinese patients with surgically resected cervical cancer. Sci Rep 2015;5:14035.

[12] Liang D, Shi S, Xu J, et al. New insights into perineural invasion of pancreatic cancer: more than pain. Biochim Biophys Acta Rev Cancer 2016;1865:111-22.
[13] Zhang G. Pay attention to the basic and clinicopathologic research of perineural invasion of cervical cancer. Chin J Obstet Gynecol 2015;50:923-5.
[14] Liebig C, Ayala G, Wilks JA, Berger DH, Albo D. Perineural invasion in cancer. Cancer 2009;115:3379-91.
[15] Wei YS, Yao DS, Long Y. Evaluation of the association between perineural invasion and clinical and histopathological features of cervical cancer. Mol Clin Oncol 2016;5:307-11.
[16] Lataifeh IM, Al-Hussaini M, Uzan C, Jaradat I, Duvillard P, Morice P. Villoglandular papillary adenocarcinoma of the cervix. Int J Gynecol Cancer 2013;23:900-5.
[17] Zhou Q, Chen H, Yang S, Li Y, Wu X. Villoglandular papillary adenocarcinoma of the uterine cervix: a report of 4 cases and a review of the literature. Oncol Lett 2016;11:837-41.
[18] Kim H, Sung J, Lee E, et al. Prognostic factors influencing decisions about surgical treatment of villoglandular adenocarcinoma of the uterine cervix. Int J Gynecol Cancer 2014;24:1299-305.
[19] Chen Y, Ho S, Liou W, Chen C. Minimal deviation adenocarcinoma of the uterine cervix. Taiwan J Obstet Gynecol 2015;54:447-9.
[20] Meng Y, Li S, Hu T, Ma D, Lu Y, Wang H. Clinical analysis of 132 cases of cervical adenosquamous carcinoma and cervical adenocarcinoma. Chin J Cancer 2010;29:15-9.
[21] Diaz De Vivar A, Roma AA, Parket KJ, et al. Invasive endocervical adenocarcinoma: proposal for a new pattern-based classification system with significant clinical implications: a multi-institutional study. Int J Gynecol Pathol 2013;32:592-601.
[22] Paquette C, Jeffus SK, Quick CM, Conaway MR, Stoler MH, Atkins KA. Interobserver variability in the application of a proposed histologic subclassification of endocervical adenocarcinoma. Am J Surg Pathol 2015;39:93-100.