Association between Silva pattern-based classification and endocervical adenocarcinoma: a systematic review and meta-analysis

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ABSTRACT

Objective To determine the relationship between the Silva pattern-based classification system and endocervical adenocarcinoma.

Methods The PubMed, Embase, Central Cochrane Library, and Web of Science databases were systematically searched for studies that investigated the correlation between the Silva classification system and the oncology prognosis or pathological features of endocervical adenocarcinoma, published in the period from January 2013 to March 2024.

Results A total of 19 eligible studies including 3122 cases were included in this systematic review and meta-analysis. The combined death rate in the Silva A, Silva B, and Silva C patterns was 0% (95% CI 0.0% to 0.4%), 2.6% (95% CI 0.4% to 5.9%), and 14.0% (95% CI 9.4% to 19.2%), respectively; the combined recurrence rate in the Silva A, Silva B, and Silva C patterns was 0.1% (95% CI 0.0% to 1.2%), 5.1% (95% CI 1.6% to 10.0%), and 19.4% (95% CI 14.7% to 24.4%), respectively; the combined lymphovascular invasion rate in the Silva A, Silva B, and Silva C patterns was 0% (95% CI 0.0% to 0.5%), 21.0% (95% CI 16.9% to 25.4%), and 58.8% (95% CI 50.1% to 67.3%), respectively; and the combined International Federation of Gynecology and Obstetrics (FIGO) I rate in the Silva A, Silva B, and Silva C patterns was 99.3% (95% CI 97.6% to 100%), 93.7% (95% CI 86.4% to 98.7%), and 82.4% (95% CI 74.9% to 88.9%), respectively.

Conclusion Our study found that Silva A was negatively correlated with death rate, while Silva C was positively correlated. There was no correlation regarding the death rate for Silva B. Based on these findings, it is suggested that the Silva pattern-based classification system can predict the prognosis of human papillomavirus (HPV)-related endocervical adenocarcinoma and assist in guiding patient treatment.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The Silva pattern-based classification was proposed to evaluate the patterns of invasion in human papillomavirus (HPV)-related endocervical adenocarcinoma and classifies endocervical adenocarcinoma as patterns A, B, and C.

WHAT THIS STUDY ADDS

⇒ This review presents data comparing the oncology prognosis of HPV-related endocervical adenocarcinoma between Silva pattern-based classes. It was found that patients with Silva C pattern have worse outcomes than those with Silva A, while the Silva B pattern shows no clear correlation with outcomes.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Using the Silva pattern-based classification enables personalized treatment plans for HPV-related endocervical adenocarcinoma. For patients with Silva A, conservative treatment may be considered, while for those with Silva C, adjuvant treatment may be more appropriate.

INTRODUCTION

Cervical cancer is the fourth most common cancer in terms of both incidence and mortality in women, with an estimated 660 000 new cases and 350 000 deaths worldwide in 2022.[1] Among them, cervical squamous cell carcinoma accounts for 80–85% of cases and endocervical adenocarcinoma accounts for 10–15%.[2] With the popularization of cervical cancer screening and the promotion of human papillomavirus (HPV) vaccination, the incidence of cervical squamous carcinoma has decreased while the incidence rate of endocervical adenocarcinoma has increased annually, accounting for 25% of all cervical cancers.[3 4]

Currently, there are some controversies and dilemmas regarding the diagnosis and treatment of endocervical adenocarcinoma.[5] First, although cervical squamous cell carcinoma and endocervical adenocarcinoma have a different histology, site of origin, and spread patterns, their staging is based on the International Federation of Obstetrics and Gynecology (FIGO) staging system, which only considers factors such as tumor size, depth of invasion and horizontal spread. However, for endocervical adenocarcinoma, numerous studies have shown that it is very difficult to correctly diagnose invasive adenocarcinoma and accurately measure the depth of invasion, and the reproducibility of depth of invasion is poor, making it difficult to distinguish adenocarcinoma in situ from endocervical adenocarcinoma.[6] Second, morphologically, endocervical adenocarcinoma is a group of heterogeneous tumors with different biological characteristics and prognosis, and the classification system of the WHO divides endocervical

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adenocarcinoma into more than 10 pathological types.[7] However, for most endocervical adenocarcinoma, the guidelines recommended by the National Comprehensive Cancer Network (NCCN) are radical surgery and nodal assessment, as well as intermediate-risk criteria, frequently referred to as Sedlis criteria, which are defined by a combination of lymphovascular space involvement, depth of stromal invasion, and tumor size.[8] These do not offer different treatment options according to the types of pathology.

Endocervical adenocarcinoma requires a different treatment strategy from cervical squamous cell carcinoma, and the management of endocervical adenocarcinoma is more complex.[9 10] Therefore, it is crucial to raise awareness about endocervical adenocarcinoma, discover prognostic factors, and establish a unique prognostic evaluation system and specific surgical decision-making process.

The Silva pattern-based classification system was proposed by Silva et al in 2013 and was further supplemented by Roma et al in 2016.[11–13] This new classification system categorizes tumors based on their invasion patterns instead of using depth of invasion and horizontal spread. There is a close correlation between different patterns and tumor biological behaviors, and this new classification is more predictive of lymphovascular invasion and tumor recurrence than FIGO staging.[11–13] According to 2024 NCCN,[8] the Silva system is used for evaluating patterns of invasion in HPV-related endocervical adenocarcinoma and classifies them as patterns A, B, or C.

There is currently a lack of comprehensive systematic reviews on this topic. Therefore, we conducted a meta-analysis and systematic review to evaluate the prognostic value of the Silva classification system in patients with HPV-related endocervical adenocarcinoma in order to guide future treatment.

Box 1 Silva pattern-based classification

Pattern A
Well-demarcated glands with rounded contours, frequently forming groups
No single cells or desmoplastic stromal reaction
Irrelevant relationship with large cervical vessels or depth of the tumor
Complex intraglandular growth allowed (ie, cribriform, papillae)
No lymphovascular invasion
Well or moderate differentiation

Pattern B
Early destructive stromal invasion arising from well-demarcated glands (pattern A-like glands) ± lymphovascular invasion

Pattern C
Diffuse destructive invasion

METHODS

Protocol Registration

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[14] Before data extraction, the review was registered with the International Prospective Register of Systematic Reviews (PROSPERO, Registration Number CRD 42023471368).

Eligibility Criteria and Exclusion Criteria

To be eligible, we aimed for the following inclusion criteria: (1) retrospective or prospective study design; (2) cases classified by Silva pattern-based classification and confirmed diagnosis of HPV-related endocervical adenocarcinoma or endocervical adenocarcinoma usual type; and (3) included articles assess at least one of the following parameters: death, recurrence, lymphovascular invasion or FIGO stage I.

We excluded studies with the following criteria: (1) reviews, letters, case reports, or editorial comments; (2) studies without full text, insufficient data or low quality scores based on the Newcastle–Ottawa Scale[15]; and (3) republished literature or repetitive studies.

Search Strategy

Two researchers (MC and LH) conducted a comprehensive search in electronic databases of PubMed, Embase, Central Cochrane Library, and Web of Science for relevant studies published from January 1, 2013 to March 21, 2024. The following search terms were used to identify relevant studies on cervical cancer: "cervical cancer", "cancer of the uterine cervix", "uterine cervical cancer", whereas the following terms were used to identify relevant studies on Silva classification: "Silva", "pattern". The search was limited to English language publications. Two researchers (MC and LH) rigorously reviewed the reference lists of all the articles to identify any potentially missing studies or unpublished data. If multiple studies analyzed overlapping patient populations, we selected the most recent or comprehensive results. After the initial selection, the full texts of all potential articles were independently read by two researchers (MC and LH) for further evaluation. Disagreements between the authors were resolved through discussion with AZ.

Data Extraction

Data were extracted independently by two investigators (LH and YW) and disagreement was resolved through discussion with AZ. The relevant data included: author, date of publication, country, cases, Silva pattern-based classification, oncology outcomes (death, recurrence), pathological features (lymphovascular invasion, FIGO stage I). We attempted to acquire missing data by contacting the authors via email. However, no replies were received.

Silva Pattern-based Classification

According to this method, HPV-related endocervical adenocarcinoma can be classified based on their 'pattern of invasion' into three groups: A, B, and C (Box 1).[12]

Oncology Outcomes

Death was calculated from the date of surgery to either the last follow-up or the date of death. Recurrence was defined as either pathological proof of cancer or an imaging study showing the regrowth of the tumor, whether confined to the pelvic region or outside it.

Pathological Features

Lymphovascular invasion is defined as the presence of tumor cells within a definitive endothelial-lined space, which can be either lymphatics or blood vessels. For endocervical adenocarcinoma,

FIGO stage I refers to cancer confined to the cervix without invading the connective tissue of the uterus or surrounding structures.

Quality Assessment

Two reviewers (MC) and (YC) independently assessed the quality of the included studies. Disagreements were resolved through discussion. All studies were assessed using the Newcastle–Ottawa Scale,[15] which is based on three categories: selected cases, comparability between groups, and outcome assessment. The total Newcastle–Ottawa Scale score was 9 points, and a score of ≥6 was conisdered high-quality literature and included in the study.

Statistical Analysis

Meta-analysis was performed using STATA 17.0 software. Subgroup analyses were based on Silva pattern-based classification and heterogeneity was determined using the orthorhombic test and I^2 statistic. If there was significant heterogeneity ($p<0.05$ or I^2 >50%), a random-effects model was used. Otherwise, a fixed-effect model was used.[16]

RESULTS

Study Selection and Characteristics

The original search retrieved a total of 1589 relevant published studies from four databases (41 from PubMed, 262 from Embase, 217 from Central Cochrane Library, and 1069 from Web of Science). After removing duplicates and screening titles and abstracts, 68 studies were retained. Then, after evaluation of the remaining full-text articles, 49 studies were excluded. Finally, a total of 19 studies[5 6 12 17–32] including 3122 patients met the inclusion criteria and were included in the meta-analysis. A flowchart of the selection process is shown in Online Supplemental Figure S1.

All studies were retrospective and all were awarded ≥7 points according to the Newcastle–Ottawa Scale criteria. The quality assessment of all studies is shown in Table 1 and the general characteristics of the studies included in this meta-analysis are summarized in Table 2.

Sub-group Analysis Based on Silva Pattern-based Classification

Death

This meta-analysis of 12 included studies[5 6 12 17 20 21 25 27–30 32] showed that the combined death rate of HPV-related endocervical adenocarcinoma was positively correlated with Silva A (effect size 0.000, 95% CI 0.000 to 0.004, I^2=0.000%, n=11), negatively correlated with Silva C (effect size 0.140, 95% CI 0.094 to 0.192, I^2=80.265%, n=12), and had no significant correlation with Silva B (effect size 0.026, 95% CI 0.004 to 0.059, I^2=52.809%, n=11) (see OnlineSupplementalFigure S2).

Recurrence

This meta-analysis of 14 included studies[5 6 12 17–21 24–28 32] showed that the combined recurrence rate of HPV-related endocervical adenocarcinoma was positively correlated with Silva A (effect size 0.001, 95% CI 0.000 to 0.012, I^2=0.000%, n=12), negatively correlated with Silva C (effect size 0.194, 95% CI 0.147 to 0.244, I^2=72.047%, n=14), and had no significant correlation with Silva B (effect size 0.051, 95% CI 0.016 to 0.100, I^2=64.107%, n=12) (see Online Supplemental Figure S3).

Lymphovascular Invasion

This meta-analysis of 16 included studies[5 6 12 17–24 26 28 30–32] showed that the combined lymphovascular invasion rate of HPV-related endocervical adenocarcinoma was positively correlated with Silva A (effect size 0.000, 95% CI 0.000 to 0.005, I^2=0.000%, n=13), negatively correlated with Silva C (effect size 0.588, 95% CI 0.501 to 0.673, I^2=90.391%, n=16), and had no significant correlation with Silva B (effect size 0.210, 95% CI 0.169 to 0.254, I^2=13.930%, n=13) (see Online Supplemental Figure S4).

FIGO Stage I

According to the eligibility studies, 13 studies[5 6 12 17–20 22 24 26 30–32] reported the association between Silva pattern-based classification and FIGO stage I. Thus, we chose FIGO stage I as one of the pathological features in our study and found that the combined FIGO stage I rate of HPV-related endocervical adenocarcinoma was positively correlated with Silva A (effect size 0.993, 95% CI 0.976 to 1.000, I^2=6.659%, n=12), negatively correlated with Silva C (effect size 0.824, 95% CI 0.749 to 0.889, I^2=89.080%, n=12), and had no significant correlation with Silva B (effect size 0.937, 95% CI 0.864 to 0.987, I^2=80.072%, n=11) (see Online Supplemental Figure S5).

DISCUSSION

Summary of Main Results

Our study indicated that patients with Silva A pattern tumors often have favorable outcomes, positively related with the oncology prognosis of endocervical adenocarcinoma, while those with Silva C tumors often have worse outcomes. Our study found no clear correlation between Silva C and the oncology prognosis of endocervical adenocarcinoma.

Results in the Context of Published Literature

This meta-analysis suggests that Silva A classification is associated with prognosis for endocervical adenocarcinoma. Roma et al[11–13] reported that 21% of patients (73/352) had pattern A tumor, all stage I, and no recurrence. These results are consistent with previous studies.[5 6 12 17 32] Genomic profiling studies have found that pattern A tumors tend to lack oncogenic changes, indicating that they may represent a less aggressive sub-set of endocervical adenocarcinoma or an early stage in tumor progression.[33] These studies support the view that patients with Silva A tumors have a good prognosis. However, Feinberg et al[34] described eight rare cases of ovarian metastases from pattern A endocervical adenocarcinoma and found a greater proportion (80%) of KRAS mutation in pattern A endocervical adenocarcinoma, which led them to think that certain gene mutations may be associated with a risk for ovarian metastases. However, the data are limited and more research is needed to understand the role of gene mutations in pattern A endocervical adenocarcinoma with metastases.

Patients with Silva A endocervical adenocarcinoma often have favorable outcomes. If a pattern A tumor persists in the cone and the margins are negative, the patient may be managed with observation; if the tumor involves the surgical margins of the cone, a second cervical conization or wider excision could be necessary;

Table 1 Quality assessment of included studies

Study	Selection				Comparability			Outcome		
	Representativeness	Selection of non-exposed	Ascertainment of exposure	Outcome not present at start	Comparability on most important factors	Comparability on other risk factors	Assessment of outcome	Long enough follow-up (median ≥5 years)	Adequacy (completeness of follow-up)	Total
Guo et al[17]	√	√	√	√	√	×	√	×	√	8
Djordjevic and Parra-Herran[18]	√	√	√	√	√	×	√	×	√	7
Devoto and Bermudez[19]	√	√	√	√	√	×	√	×	√	7
Byun et al[20]	√	√	√	√	√	×	√	×	√	7
Wu et al[21]	√	√	√	√	√	×	√	×	√	7
Salvo et al[22]	√	√	√	√	√	×	√	×	√	8
Xu et al[23]	√	√	√	√	√	×	√	×	√	7
Alvarado-Cabrero et al[24]	√	√	√	√	√	√	√	×	√	7
Stolnicu et al[25]	√	√	√	√	√	×	√	√	√	8
Spaans et al[6]	√	√	√	√	√	×	√	×	√	7
Sharma et al[26]	√	√	√	√	√	×	√	×	√	7
Roma et al[12]	√	√	√	√	√	×	√	×	√	7
Rivera-Colon et al[27]	√	√	√	√	√	×	√	×	√	7
Roma et al[28]	√	√	√	√	√	×	√	×	√	7
Li et al[29]	√	√	√	√	√	×	√	√	√	8
Li et al[30]	√	√	√	√	√	×	√	√	√	8
Stolnicu et al[31]	√	√	√	√	√	×	√	×	√	7
Wang et al[5]	√	√	√	√	√	×	√	×	√	7
Li et al[32]	√	√	√	√	√	×	√	×	√	7

Table 2 Basic characteristics of included studies

First author	Year	Study period	Region	Study design	Cases	Quality
Guo et al[17]	2022	Jan 2006–Dec 2017	China	Retrospective	345	8
Djordjevic and Parra-Herran[18]	2016	Not mentioned	Canada	Retrospective	47	7
Devoto and Bermudez[19]	2019	Not mentioned	Argentina	Retrospective	32	7
Byun et al[20]	2019	Jan 2005–Dec 2016	Korea	Retrospective	76	7
Wu et al[21]	2023	2010–2018	China	Retrospective	84	7
Salvo et al[22]	2019	Not mentioned	Italy	Retrospective	235	9
Xu et al[23]	2019	Dec 2006–March 2017	China	Retrospective	201	7
Alvarado-Cabrero et al[24]	2017	Not mentioned	USA Mexico et al	Retrospective	189	7
Stolnicu et al[25]	2021	1985–2019	USA Romania et al	Retrospective	388	8
Spaans et al[6]	2018	Jan 1990–Dec 2011	Netherlands	Retrospective	82	7
Sharma et al[26]	2023	2002–2018	Canada, USA	Retrospective	45	7
Roma et al[12]	2016	Not mentioned	USA, Mexico and others	Retrospective	352	7
Rivera-Colon et al[27]	2021	2001–2019	USA	Retrospective	80	7
Roma et al[28]	2017	Not mentioned	Mexico and others	Retrospective	127	7
Li et al[29]	2023	Jan 2010–Sept 2021	China	Retrospective	124	8
Li et al[30]	2022	Jan 2009–Dec 2017	China	Retrospective	120	8
Stolnicu et al[31]	2018	Not mentioned	Romania, Canada and others	Retrospective	341	7
Wang et al[5]	2018	Not mentioned	China	Retrospective	191	7
Li et al[32]	2022	Mar 2011–Dec 2016	China	Retrospective	63	7

if the margin of the second surgery shows a Silva B or C pattern, treatment should be followed based on the result of the second surgery. Moreover, according to this new system, one does not need to distinguish between adenocarcinoma in situ and pattern A endocervical adenocarcinoma as they undergo the same treatment and have an excellent prognosis,[12] addressing the problem mentioned in some studies that a clear distinction between endocervical adenocarcinoma and adenocarcinoma in situ is not possible in up to 20% of cases.[35 36]

We also found that Silva C classification was negatively associated with the prognosis of endocervical adenocarcinoma. Roma et al[12] reported that 53.7% of patients (189/352) had a pattern C tumor, with 61.9% of patients showing evidence of lymphovascular invasion, 21.5% patients had recurrence, and 9.5% (18/189) died from the disease. These results were similar to those of other studies.[5 6 12 17 32] However, Alvarado-Cabrero et al[24] divided 189 patients with pattern C endocervical adenocarcinoma into six groups and found that not all pattern C endocervical adenocarcinoma had an aggressive behavior. Xu et al[23] stratified pattern C tumors into four sub-groups and found that different growth patterns showed variations in the risk of lymphovascular invasion. A study based on genomic profiles reported that pattern B and pattern C tumors have multiple oncogenic mutations such as PIK3CA, KRAS, and ERBB2.[33] Given these findings, it is recommended that patients with Silva C tumors, characterized by diffuse destructive stromal invasion, should undergo adjuvant treatment.[12]

Our review of available studies suggests that there is no clear link to prognosis in patients with Silva B tumors, leading to more uncertainty in their treatment. Roma et al[11–13] reported that only four of 90 patients with pattern B tumors had lymphovascular invasion. All patients had clinical stage I tumor and only one patient experienced a vaginal recurrence. Similar findings were reported in other studies,[5 6 12 17 32] supporting the view that the Silva B classification is relatively uncertain. In addition, Sharma et al[26] found that pattern B tumors with lymphovascular invasion clustered with pattern C, whereas pattern B tumors without lymphovascular invasion approached pattern A genotypically. They consolidate the Silva classification into low-risk (pattern A and pattern B without lymphovascular invasion) and high-risk (pattern B with lymphovascular invasion and pattern C) and found that high-risk tumors were enriched in mutations in PIK3CA, ATRX, and ERBB2.

Thus, the characteristic of Silva B tumors is focal destructive stromal invasion, mainly from tumor glands of Silva A structure, with or without lymphovascular invasion. Therefore, on the basis of cold knife conization, loop electrosurgical excision, or cervical resection, lymph node sampling should be performed simultaneously. As suggested by Roma et al, if sentinel lymph nodes are positive or reassessed as Silva C, radical hysterectomy should be chosen and lymph node dissection and post-operative radiotherapy and chemotherapy should be performed as appropriate.[12] Patients with reassessed pattern A only need follow-up.[12]

The prognostic value of the Silva classification for HPV-related endocervical adenocarcinoma is controversial, with some studies showing a correlation with overall survival and disease-free survival while others report no correlation. Thus, further studies are warranted for investigating the correlation between the Silva pattern-based classification and HPV-related endocervical adenocarcinoma. According to Zeng et al,[37] multivariate analysis showed

that the Silva pattern system provided independent risk factors for prognosis. However, Li et al[30] found that the Silva classification showed no correlation with overall survival and disease-free survival and concluded that it is helpful for selecting the appropriate operation before surgery but that its prognostic value requires further evaluation.

In a prior study, Li et al[29] concluded that the Silva classification system could predict the lymph node status and prognosis of HPV-related endocervical adenocarcinoma, but that it cannot be used alone as a guideline for treatment and prognosis and should be combined with the patient's clinical stage and other high-risk factors. Therefore, based on Silva pattern-based classification, some researchers tried to establish new models to guide the treatment of HPV-related endocervical adenocarcinoma. Li et al[32] presented a second-generation system called the Silva cumulative score, and provided evidence for its potential value to predict overall survival and disease-free survival in HPV-related endocervical adenocarcinoma. They suggested that the Silva cumulative score system could be useful for more precise therapeutic trials in HPV-related endocervical adenocarcinoma. Guo et al[17] reported a Silva-based 4-factor model (Silva C, ≥3 cm, depth of stromal invasion >2/3, and >mild lymphovascular invasion) specifically for patients with intermediate-risk endocervical adenocarcinoma which has a superior recurrence prediction performance to the Sedlis criteria, so it may better guide post-operative adjuvant therapy.

Strengths and Weaknesses

To the best of our knowledge, this is the first meta-analysis to focus on the relationship between the Silva pattern-based classification and oncology prognosis, and pathological features of HPV-related endocervical adenocarcinoma. However, this study has several limitations. One potential weakness is that all the included studies were retrospective, which inherently comes with some limitations. Additionally, the included studies had varying follow-up periods, making it difficult to accurately analyze 5-year overall survival or disease-free survival. Furthermore, we only included studies conducted in English, which potentially introduces language bias into our findings.

Implications for Practice and Future Research

According to the Silva classification, patients with Silva A and B endocervical adenocarcinoma can avoid radical hysterectomy and those with a Silva A diagnosis can retain fertility. Therefore, we recommend adding the Silva classification to the pathological report of endocervical adenocarcinoma, which would have a significant impact on the treatment of young patients, particularly for women of reproductive age who require fertility preservation, and also to avoid overtreatment in patients with a good prognosis. However, since the Silva classification is still at a developmental stage, further prospective data and continued testing will be necessary to better facilitate its use in routine clinical practice in the future.

CONCLUSION

Based on the evidence provided, there is an association between prognostic value, pathological features, and the Silva A and C patterns of endocervical adenocarcinoma, while the association with the Silva B pattern remains uncertain. According to the treatment of the Silva pattern-based classification, it can reduce overtreatment and complications by assessing tumor cell growth patterns and creating personalized treatment plans for HPV-related endocervical adenocarcinoma. However, further prospective studies are needed to determine the oncological prognostic value and its impact on clinical decision-making.

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