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Villoglandular pattern in HPV-associated endocervical adenocarcinoma is associated with excellent prognosis: a reappraisal of 31 cases using IECC and Silva Pattern Classification

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Abstract

Villoglandular adenocarcinoma (VGA) of the cervix is a rare histologic entity that typically develops in young women, characterized by an association with oral contraceptives and excellent prognosis, though this point is controversial. These tumors have not been studied in the context of the International Endocervical Adenocarcinoma Criteria and Classification (IECC) or Silva Pattern Classification (SPC).

We analyzed 31 cases that met strict diagnostic criteria, including being completely excised with negative margins. These were categorized according to IECC and SPC and the association with various pathologic parameters analyzed.

Most patients were young with a mean age of 41.1 (range 25-79). There were 14 (45.2%) Pattern A, 11 (35.5%) Pattern B and 6 (19.3%) Pattern C cases. Only 1 of 22 patients (4.5%) presented with lymph node metastasis (LNM) at the time of diagnosis (Pattern C, stage IB1) and 3 (9.7%) had lymphovascular invasion (LVI) (2 Pattern C, 1 Pattern B). Overall survival was 100%, while recurrence free survival (RFS) was 96.2% for the entire cohort with only 1 case (3.2%) recurring 25 months after surgery (IB2, Pattern B). Kaplan Meier analysis (log rank test) revealed no significant correlation for RFS at 5 and 10 years associated with depth of invasion, tumor size, Silva pattern, FIGO stage, LVI or LNM. Cox univariate analysis demonstrated no independent prognostic factors predicting RFS.

These results indicate that completely excised VGA generally has excellent prognosis and when Silva Pattern Classification is applied, those tumors that potentially have a higher chance for adverse outcomes can be identified.

Keywords

villoglandular pattern; endocervical adenocarcinoma; Silva classification; prognosis; management

Introduction

Villoglandular adenocarcinoma (VGA) of the cervix is a distinct entity first described by Young and Scully in 1989 in which they reported 13 cases with excellent outcomes[1]. These tumors tended to occur in younger women and due to the indolent behavior, the authors suggested that they could be treated less radically than conventional endocervical adenocarcinoma (ECA). A subsequent report by Jones et al. suggested an association between oral contraceptive (OCP) use and VGA since 15 of 24 patients had a history of OCP use compared to only 5 of 18 in the control group[2]. Since then, there have been several case reports and series describing VGA with mostly good outcomes; however, there have also been many cases of so-called VGA with lymph node metastases, recurrences and even deaths[2–10]. This raises three important questions: 1) Is this a truly distinct tumor with good outcomes that justifies more conservative therapy? 2) Were strict diagnostic criteria applied

in these studies according to the original description? 3) Can these tumors be diagnosed accurately and consistently?

In addition, since the original description of VGA, there has been a major paradigm shift in the classification of ECAs based on the International Endocervical Adenocarcinoma Criteria and Classification (IECC) study[11]. Rather than using pure histologic appearance, ECAs are now classified by the World Health Organization (WHO) according to clinically meaningful groups based on their etiological association with human papillomavirus (HPV) infection into HPV-associated (HPVA) and HPV-independent (HPVI)[11,12]. The most common type of ECA is HPVA usual type and two specific architectural patterns are recognized as part of the usual type spectrum: villoglandular and micropapillary. While the micropapillary pattern has been recently described as being highly aggressive, the prognosis of villoglandular pattern has been a source of debate since its original description[13]. This may be due, in part, to the lack of adherence to strict diagnostic criteria as originally described by Young and Scully[1]. Villoglandular adenocarcinomas are characterized by two main features: 1) predominant exophytic papillary architecture and 2) tumor cells showing no more than mild to moderate nuclear atypia[1,11,12]. While there can be some desmoplastic stromal infiltration at the base, it should not be extensive, and there can be no component that is architecturally poorly differentiated or has high nuclear grade[11,12]. Importantly, conservative therapy is only recommended in the setting of no more than superficial destructive invasion, no lymphovascular invasion (LVI) and complete excision with negative margins (cone or hysterectomy). The IECC study used strict criteria for the diagnosis of VGA and in that original cohort, only 2 out of more than 300 cases qualified as having villoglandular pattern; both were positive for p16 and HPV and were associated with good prognosis (no LVI, lymph node involvement, recurrences or death after 86 and 155 months)[11]. The association of VGA with high-risk HPV has also been previously reported[14,15].

Another recent major development in the classification of HPVA ECAs is the Silva Pattern Classification System that uses histologic pattern of invasion to assign risk of lymph node metastasis (LNM) and recurrence regardless of stage[16]. To the best of our knowledge, there have been no studies assessing the prognosis of cervical VGAs in the context of the IECC and Silva Pattern Classification system.

Therefore, we sought to analyze endocervical adenocarcinomas with villoglandular pattern contributed from various international institutions to assess morphology, association with HPV infection and prognosis. Specifically, we applied strict diagnostic criteria and separated VGA into pure versus mixed tumors using Silva Pattern Classification in order to identify potential prognostic parameters in the context of invasive patterns and provide evidence-based recommendations for the management of these tumors.

Materials and Methods

This study was approved by the institutional review boards of each participating center.

Case selection

Forty-four cases of ECAs with villoglandular pattern were initially contributed from 12 international institutions and retrospectively analyzed (University of Medicine, Pharmacy, Sciences and Technology, Targu Mures, Romania; Hospital Garcia de Orta, Almada, Portugal; University Hospital of Saint-Etienne, France; The University of British Columbia, Vancouver, British Columbia, Canada ; Instituto Portugues de Oncologia, Lisbon, Portugal; Sahlgrenska University Hospital, Gothenburg, Sweden; University of Cagliari, Sardinia, Italy; Hospital Universitari Vall d'Hebron, Barcelona, Spain; Hospital Universitario La Paz, Madrid, Spain; University of Health Sciences, Istanbul, Turkey; Centro Hospitalar de Vila Nova de Gaia Espinho, Porto, Portugal; Memorial Sloan Kettering Cancer Center, New York, USA). Two of the 44 cases were retrieved from the original IECC database published in 2018, while the remaining cases were added subsequently[11]. A spreadsheet was created to capture clinico-pathologic and follow-up data and shared with all participants of the study. The types of specimens included were large loop excision of the transformation zone (LLETZ), conizations, trachelectomies, and simple/radical hysterectomies with or without lymph node samples. Complete excision of the tumor with negative margins was required. Biopsies were excluded.

Participants submitted representative sections from their cases as either glass slides or whole slide images (WSI) for central review by the first and senior authors (SS and KJP) who reviewed the cases via video link and shared screen. The two IECC cases were reviewed as previously published: hematoxylin and eosin (H&E) slides containing tumor were examined at a multi-headed microscope and a consensus diagnosis was reached among three pathologists (RAS, KJP, and SS) for each case[11].

Morphologic assessment

All cases were classified according to IECC into HPVA and HPVI ECAs[11]. Briefly, the HPVA tumors are characterized by easily identifiable apical mitotic figures and apoptotic bodies at scanning or intermediate magnification. This approach has been previously validated by p16 immunohistochemistry, high-risk HPV mRNA in situ hybridization, and external validation studies[11,17,18]. The following features were required to be classified as having villoglandular pattern: 1) prominent exophytic papillary architecture in the superficial portion of the tumor with papillae of variable thickness and length containing central fibrous cores 2) lined by pseudostratified glandular cells exhibiting no more than low-to-moderate nuclear atypia [Figure 1A–1C]. A component of non-villoglandular usual type adenocarcinoma was defined as stromal infiltrating glands of various sizes and shapes lined by pseudostratified, elongated and hyperchromatic nuclei with numerous mitotic figures and apoptotic bodies at scanning magnification [Figure 1D][11]. Tumors with only superficial papillary architecture and no destructive invasion into the cervical stroma were categorized as pure villoglandular pattern consistent with Pattern A [Figure 1A]. Non-destructive stromal invasion was permissible and when present was the basis for measuring depth of invasion (DOI) [Figure 2A–B]. In contrast, tumors with superficial papillary architecture and areas of destructive cervical stromal invasion regardless of DOI were diagnosed as mixed villoglandular pattern. Those with mixed villoglandular pattern were subsequently designated as Pattern B (early/limited destructive stromal invasion by

small clusters or individual tumor cells in a focally desmoplastic stroma in a background of pattern A) [Figure 2C–D] or Pattern C (diffuse destructive stromal invasion with associated desmoplastic stromal reaction) [Figure 2E–F].

Ancillary studies for p16 immunohistochemistry and HPV in situ hybridization were performed either in routine work up or as part of the present study. p16 was interpreted as positive if diffuse strong nuclear and cytoplasmatic staining was present, whereas no or patchy staining was interpreted as negative. HPV in situ hybridization (ISH) with a chromogen was performed using Advanced Cell Diagnostics RNAscope System (catalog no. 312598). The RNAscope HPV HR18 contains probes targeting E6 and E7 mRNA for the following 18 high-risk subtypes: HPV16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73 and 82. The method and interpretation were previously described in full detail[11].

The following parameters were retrieved from the clinical files of each institution: age, past medical history, 2018 FIGO stage, surgical treatment, adjuvant treatment, size, DOI, LNM, local or distant recurrences, and survival. Data regarding the use of oral contraceptives was not available. Overall survival (OS) was defined as the time from surgery until death by any cause. Recurrence free survival (RFS) was defined as the length of time after primary treatment ended for which the patient survived without any signs or symptoms of cervical cancer. In addition, full slide sets were used to determine the presence of Silva pattern of invasion and LVI.

Statistical analysis

Data were tabulated using Microsoft Excel software and analyzed using SPSS for Microsoft Windows, version 20.0 (Chicago, IL, USA). The Kaplan-Meier test was used for survival curve estimates; and the log-rank Mantel Cox test was used for group comparisons. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using the Cox proportional hazards regression model, in univariate analyze. $P<0.05$ was considered statistically significant.

Results

Of the 44 initially submitted cases, only 31 met diagnostic criteria for villoglandular pattern, the clinico-pathologic data of which are included in Table 1. Thirteen cases were excluded because of non-VGA histology after review. Mean age was 41.1 years (median 40; range 25-79) with 27 patients (87.1%) under 50 and 4 patients (12.9%) 50 years of age or older. Eight patients (25.8%) were treated with cone, while 23 (74.2%) underwent simple or radical hysterectomy. Only 1 (4.5%) of the 22 patients with lymph node dissection presented with LNM at the time of diagnosis, a stage IB1 tumor (8 mm DOI) with mixed villoglandular pattern C and positive LVI. Four of 27 patients (14.8%) received adjuvant therapy (chemoradiation), while information on adjuvant therapy was not available for 4 patients.

Tumor size was available in 29 of 31 cases and ranged from 3 to 40 mm with mean a of 23 mm. The 2018 FIGO stage breakdown was as follows: 5 (16.1%) IA1, 2 (6.5%) IA2, 20 (64.5%) IB1 and 4 (12.9%) IB2. Fourteen tumors (45.2%) showed Silva pattern A and

were classified as pure villoglandular pattern, while 17 (54.8%) were Silva pattern B or C and classified as mixed villoglandular pattern, of which 11 were pattern B (35.4%) and 6 pattern C (19.4%). Twenty (64.5%) tumors had DOI ≤5 mm, while 11 (35.5%) had DOI >5 mm (DOI range: 0.7-17 mm). Only 3 cases (9.7%) had LVI, all of which were mixed villoglandular pattern (2 pattern C, 1 pattern B). The remaining 28 (90.3%) did not have LVI. No cases presented with extension into the endometrium, fallopian tubes or ovaries. All 13 (100%) cases tested for p16 and all 5 (100%) tested for HPV were positive.

The mean follow-up period was 84 months (1-240 months) and only 1 (3.2%) patient recurred in the rectouterine pouch 25 months after initial radical hysterectomy with salpingo-oophorectomy and lymph node dissection. This was a stage IB2 (30 mm tumor diameter, with 10 mm DOI) mixed villoglandular tumor, pattern B, with no LVI or LNM.

Overall survival was 100% and RFS was 96.2% for the entire cohort (31 cases). Kaplan Meier analysis (log rank test) revealed no statistically significant correlation between RFS at 5 and 10 years with DOI (Figure 3A), Silva pattern of invasion (Figure 3B), FIGO stage (Figure 3C), presence of LVI (Figure 3D) and LNM Figure 3E) (p=0.243, p=0.429, p=0.584 p=0.718 and p=0.841 respectively).

Cox univariate analysis comparing the clinico-pathologic parameters age (p=0.816), FIGO stage (p=0.737), surgical treatment (p=0.715), DOI (p=0.589), Silva pattern (p=0.657), presence of LVI (p=0.816), and presence of LNM (p=0.895) demonstrated no independent prognostic factors predicting RFS (Table 2).

Discussion

In the original description of endocervical villoglandular adenocarcinoma by Young and Scully, the authors state that this term should be reserved for tumors in which the villoglandular component is the “exclusive or almost exclusive” pattern[1]. Several of their cases showed stromal invasion, including into the deep cervical wall, and one case even invaded into the endometrium and myometrium, yet they all had uniformly good clinical outcomes and the authors suggested these tumors could be treated less radically than conventional cervical adenocarcinoma. Interestingly, they describe the stromal invasive component as having the same fibromatous stroma as in the superficial papillae but occasionally with desmoplastic stroma. Their figure 3 would now be classified as Silva Pattern A, while figure 4 would now be either B or C. However, in the subsequently published studies and case reports of VGA, there has been inconsistent application of these criteria for defining VGA and therefore, the outcomes have also been inconsistent. Cases of recurrence and even death in purported cases of VGA have been reported[2–10]. In the era of Silva pattern classification, we aimed to categorize VGA into those with pure villoglandular morphology without destructive invasion (pattern A) and those with a component of destructive stromal invasion (patterns B and C) and determine outcomes.

Villoglandular adenocarcinoma is comprised of a superficial, exophytic, papillary component with long and thin or occasionally short and thick fibrovascular cores lined by columnar epithelium with scant mucin, nuclear pseudostratification, mitotic figures and

no more than mild to moderate nuclear atypia. There is typically no or only superficial destructive stromal invasion. In the present study, we have attempted to apply strict criteria in the diagnosis of pure versus mixed villoglandular pattern, by combining IECC with Silva pattern classification. As defined per IECC and in this study, pure VGA shows no destructive stromal invasion and is always Silva pattern A, while mixed VGA harbors destructive stromal invasion and is classified as Silva pattern B or C. Of the 44 cases initially collected, only 31 met these criteria, with 14 (45.2%) pure and 17 (54.8%) mixed, the remaining 13 excluded based on non-VGA histology.

We demonstrated that only mixed cases had the potential to metastasize or recur (though this potential was very low), while pure villoglandular tumors were not associated with LVI, LNM or recurrence. The one patient with lymph node involvement at the time of initial surgery had a stage IB1 tumor (8 mm DOI) with mixed Pattern C and positive LVI. The patient with pelvic recurrence 25 months after initial surgery had a stage IB2 tumor (10 mm DOI) mixed Pattern B without LVI or LNM. Interestingly, the recurrence location in this particular case may be due to contamination during surgery and the type of surgery rather than tumor biology[19–21]. We found no statistically significant difference in OS (100% for both categories) and RFS (100% versus 93.8%) between pure versus mixed VGA, respectively. Kaplan Meier analysis (log rank test) revealed no statistically significant correlation between OS and RFS at 5 and 10 years with any prognostic parameter, while Cox univariate analysis comparing clinico-pathologic parameters demonstrated no independent prognostic factors predicting RFS. Although these data suggest that VGA has excellent prognosis regardless of tumor size, FIGO stage or DOI, our numbers are small, and it is clear that tumors with diffuse destructive invasion and/or LVI are the most concerning for adverse outcomes.

We also found that most villoglandular pattern tumors occurred in young women (mean age 41.1 years) with 27 patients (87.1%) under 50 years of age. Unfortunately, we did not have access to any history of oral contraceptive use. Most tumors were large (mean size of 23 mm) and though not explicitly stated, likely clinically visible. Only 5 (16.1%) were stage IA1. Consequently, 8 patients (25.8%) were treated with cone, while the remaining 23 (74.2%) received simple or radical hysterectomy, with all but one (22/23, 71%) undergoing pelvic lymph node sampling. Of the 22 patients with lymph node dissection, only 1 (4.5%) presented with LNM at diagnosis (mixed Pattern C with LVI).

The results of this study indicate that tumors with either pure or mixed villoglandular pattern have excellent prognosis when completely excised with negative margins. These results are similar to those of Guo et al, as well as to a recently published review and meta-analysis of 271 patients, both confirming no deaths and low recurrence rates in cases with villoglandular pattern and superficial invasion[22,23]. In our series, 11 (35.5%) tumors had more than superficial invasion with DOI >5 mm, only 2 of which metastasized/recurred. The case with LNM had 8 mm DOI, pattern C, while the case with recurrence had 10 mm DOI, pattern B. The generally favorable prognosis regardless of DOI or type of procedure (cone vs hysterectomy) suggests that a more conservative approach is acceptable, especially since these tumors tend to develop in young patients who may wish to maintain fertility. The inconsistencies in the literature regarding the indolence of VGA may be related to

the lack of adherence to strict diagnostic criteria regarding the presence and amount of destructive invasion since none has ever been previously provided. Based on our findings and in line with prior studies of Silva pattern classification, it seems that pure VGA (no destructive invasion, no LVI) has excellent outcomes and can be treated conservatively, regardless of tumor size or stage. On the other hand, while mixed VGA with varying degrees of destructive stromal invasion also seem to have generally good outcomes, these are better treated based on pattern of invasion and the presence of LVI, such that those with pattern C and/or LVI should have more extensive surgical resection and lymph node sampling. Therefore, we recommend that cervical "adenocarcinoma with villoglandular pattern," terminology endorsed by the 2020 WHO classification, be reserved only for those tumors with pure villoglandular morphology without destructive invasion (non-destructive stromal invasion is permissible). For those tumors with villoglandular pattern mixed with destructive invasion, we recommend diagnosing these cases as usual type along with the pattern of invasion and LVI status so that the most appropriate treatment can be undertaken based on individual patient factors.

In this study of 31 ECAs with predominant villoglandular morphology, we have shown that these tumors are a morphologically distinct variant of HPVA adenocarcinoma with excellent outcomes that often affect young women of child-bearing age. A conservative surgical approach may be acceptable even for large clinically visible tumors without destructive invasion.

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Availability of data and material:

All data can be provided by the corresponding author (Simona Stolnicu)

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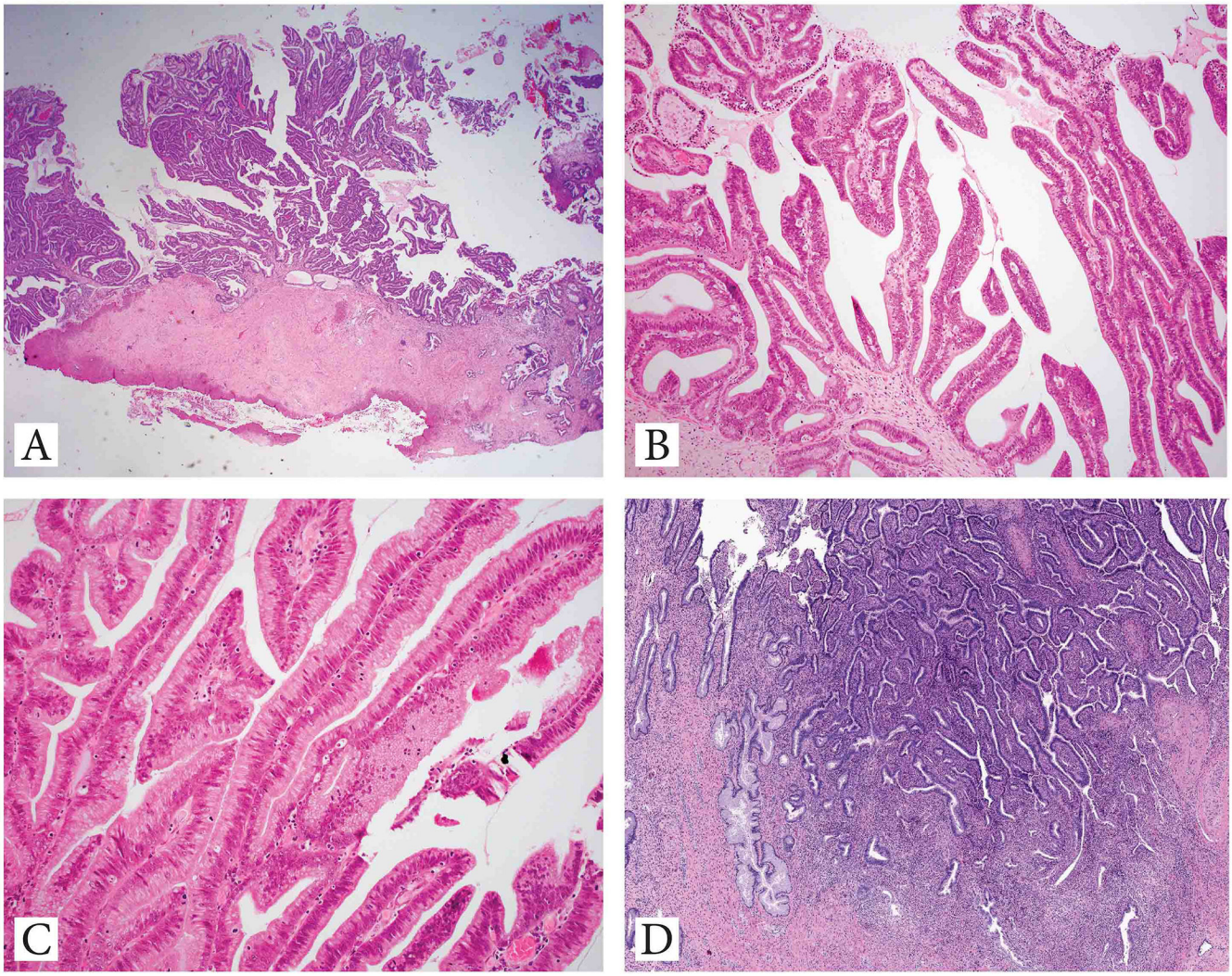

Figure 1:

A. Prominent villoglandular exophytic pattern with long slender papillae, short papillae, fibrovascular cores (low and intermediate power)

B. Low to moderate nuclear atypia (intermediate power)

C. Low to moderate nuclear atypia (high power)

D. Non-villoglandular portion (usual type) with irregularly shaped glands infiltrating stroma (low power)

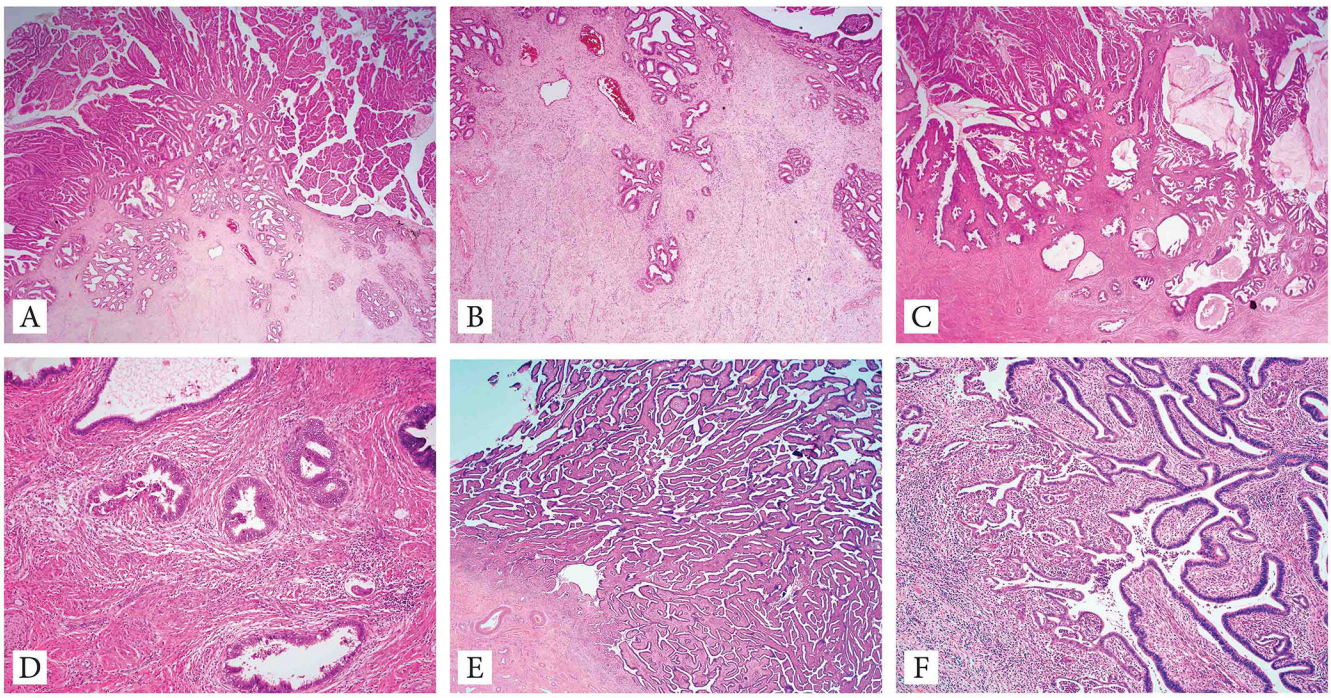

Figure 2:

A. Pure villoglandular adenocarcinoma with Pattern A nondestructive stromal invasion, low power

B. Pure villoglandular adenocarcinoma with Pattern A nondestructive stromal invasion, high power of non-destructive stromal invasion

C. Mixed villoglandular adenocarcinoma, Pattern B (low power)

D. Mixed villoglandular adenocarcinoma, Pattern B showing focal destructive invasion (high power)

E. Mixed villoglandular adenocarcinoma, Pattern C (low power)

F. Mixed villoglandular adenocarcinoma, Pattern C (intermediate power)

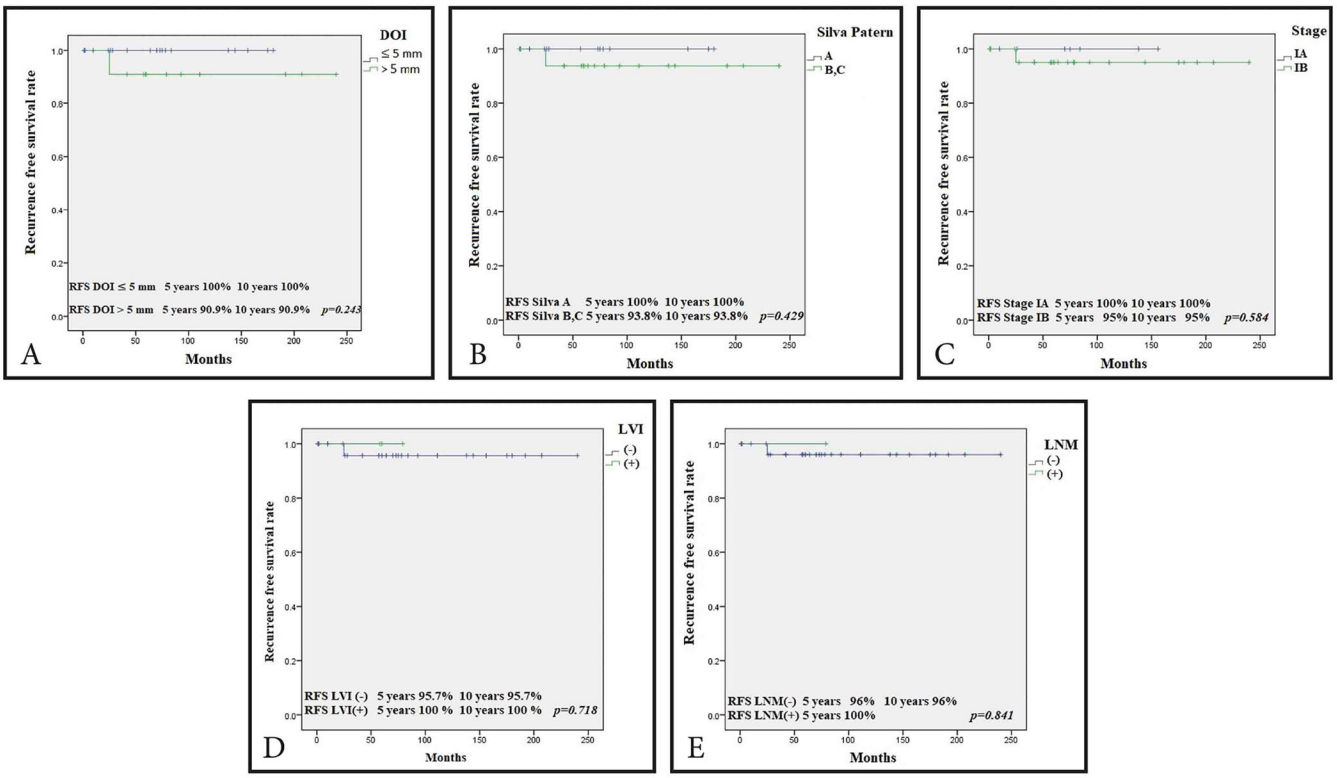

Figure 3.

A. Kaplan-Meier RFS 5 and 10 years: DOI

B. Kaplan-Meier RFS 5 and 10 years: Silva Pattern

C. Kaplan-Meier RFS 5 and 10 years: FIGO stage

D. Kaplan-Meier RFS 5 and 10 years: LVI

Kaplan-Meier

Table 1:

Clinical and pathological parameters of 31 villoglandular ECAs

Clinico-pathologic parameters	Villoglandular ECAs
	N (cases), %
Total	31
Age Mean, Median (year)	41.1(40)
Std. Deviation, Range	9.91(25-79)
Age <50 years	27(87.1%)
≥50 years	4(12.9%)
Surgical Treatment Cone	8(25.8%)
Surgical Treatment Hysterectomy	23(74.2%)
LN dissection	22(71%)
p16 positivity (diffuse strong)	13(100%)
HPV positivity	5(100%)
FIGO Stage IA1	5(16.1%)
FIGO Stage IA2	2(6.5%)
FIGO Stage1B1	20(64.5%)
FIGO Stage1B2	4(12.9%)
DOI ≤ 5mm	20(64.5%)
DOI > 5 mm	11(35.5%)
Tumor size range (mm)	3-40 (mean 23)
Silva pattern A	14(45.2%)
Silva pattern B	11(35.4%)
Silva pattern C	6 (19.4%)
LVI positive	3(9.7%)
LVI negative	28(90.3%)
Regional /remote lymph node metastasis Yes	1(4.5%)
Regional /remote metastasis No	21(95.5%)
Recurrences Yes	1(3.2%)
Recurrences No	30(96.8%)

Abbreviations: ECA: endocervical adenocarcinoma; LN: lymph node; HPV: Human Papillomavirus; DOI: depth of invasion; LVI: lympho-vascular invasion

Table 2:

Cox regression univariate analysis on 31 cases of villoglandular adenocarcinomas

	HR	CI	p value
Age	24.23	0.01-1115.13	0.816
FIGO stage IA vs IB	30.25	0.01-1296.60	0.737
Surgical treatment	32.91	0.01-448.29	0.715
DOI	93.08	0.01-127.15	0.589
Silva pattern A vs B/C	44.17	0.01-798.67	0.657
LVI present	0.041	0.01-1899.16	0.816
LNM present	21.31	0.01-1031.21	0.895

Abbreviations: DOI: depth of invasion; LVI: lympho-vascular invasion; LNM: lypmh node metastases