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Prevalence and Clinicopathologic Features of HER2 Overexpression in Endocervical Adenocarcinoma

Niusha Momeni[*], MD, Fatemeh Nili[*♦], MD, Fereshteh Ameli[*], MD, Soheila Sarmadi[**], MD, Elham Mirzaian[***], MD, Farnaz Moravej-Salehi[**], MD, Narges Zamani[****], MD

[*]*Department of Pathology, Cancer Institute, Imam Khomeini Hospital Complex, Faculty of Medicine, Tehran University of Medical Sciences, Tehran, Iran*
[**]*Department of Pathology, Yas Hospital Complex, Faculty of Medicine, Tehran University of Medical Sciences, Tehran, Iran*
[***]*Department of Pathology, Dr Shariati Hospital Complex, Faculty of Medicine, Tehran University of Medical Sciences, Tehran, Iran*
[****]*Department of Gynecology Oncology, Imam Khomeini Hospital Complex, Faculty of Medicine, Tehran University of Medical Sciences, Tehran, Iran*

♦**Corresponding Author**
Fatemeh Nili, MD
Department of Pathology,
Cancer Institute, Imam Khomeini Hospital Complex,
Faculty of Medicine, Tehran University of Medical Sciences,
Tehran, Iran
Email: f.nili@sina.tums.ac.ir

Abstract

Background: Endocervical adenocarcinoma (ENCA) has poor prognosis and is increasing in developing countries. Human epidermal growth factor receptor 2 (HER2) overexpression in ENCA is not fully known. The aim of this study was to assess the prevalence and clinicopathological features of HER2 overexpression in ENCA.

Method: In this cohort study, 48 ENCA cases were reclassified using the World Health Organization (WHO) classification. Whole-tissue sections were stained for HER2 by immunohistochemistry (IHC) and scored using 2017 American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) protocol (negative= 0, 1+, equivocal= 2+, and positive= 3+). Fluorescent in situ hybridization (FISH) assay was performed for 2+ stained cases. Invasion growth pattern and clinicopathologic features were investigated. Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) and Statistical software for data science (STATA) with chi square, Fischer exact, independent sample t-test, and one-way Analysis of Variance (ANOVA) at 0.05 significance level.

Results: 16.6% of ENCAs overexpressed HER2, IHC3+ (n=6) and IHC2+ (n=2). No human papilloma virus (HPV)-independent case was found. HER2 was expressed in half of the invasive stratified mucin-producing carcinomas (ISMICs) ($P < 0.05$) and was not associated with stage,

metastasis, lymph-vascular space invasion, lymph node metastasis, or pattern of invasion pattern ($P > 0.05$).
Conclusion: ENCAs, including HPV-associated subtypes, overexpress HER2 in about 16.6% of the cases. Overexpression in ISMIC is significantly higher than the other subtypes, which can be considered for therapeutic trials in this histopathologic subcategory.
***Keywords**:* Uterine cervical neoplasms, HER2 protein, Immunohistochemistry, Prognosis

Introduction

Cervical cancer is the fourth most prevalent malignancy among females.[1] Squamous cell carcinoma (SCC) is the most common cervical cancer, which is caused by human papilloma virus (HPV) infection as the main primary etiology. However, cervical adenocarcinoma incidence is observed to be increasing, especially in developing countries, constituting approximately 25% of cases.[2–3] Notably, cervical adenocarcinomas demonstrate a worse prognosis as compared with SCCs due to their tendency for early local invasion, lymph node metastasis, and resistance to conventional chemotherapy.[4]

A new classification for cervical adenocarcinomas has been developed, dividing them into two distinct groups based on their association with HPV infection. HPV-associated endocervical adenocarcinoma (ENCA) is significantly noted at younger ages than HPV-independent. Histologically, all HPV-associated ENCAs were categorized into three groups based on the pattern of invasion using the SILVA system. The SILVA classification can provide the probability of lymph node metastasis, recurrence rate, and overall survival based on tumor growth and invasion pattern. In contrast to HPV-associated ENCAs, all types of HPV-independent ENCAs have more aggressive behavior and a destructive pattern of invasion, leading to an increased risk of distant metastasis and an advanced clinical stage at disease onset. Therefore, the prognosis of this subtype indicates lower survival rates. The gastric subtype stands as the most common form of HPV-independent ENCA and usually occurs between the ages of 50 and 55 on average, constituting 10–15% of HPV-independent cervical cancers.[5]

Due to the worse prognosis of ENCA and the increasing incidence rate and resistance to chemoradiotherapy in comparison with SCC of the uterine cervix, there is a pressing need for discovering new diagnostic markers and therapeutic targets to improve the disease prognosis and treatment outcomes.[6] The oncogenic role of the overexpression of epidermal growth factor receptor (EGFR) family markers is confirmed and has been proposed as a potential etiological factor in cervical cancer. Recent investigations show the overexpression of various EGFR family markers, such as receptor tyrosine kinase, EGFR, HER2, and mesenchymal epithelial transformation proto-oncogene (C-met), in cervical adenocarcinoma, which has revealed an association with an unfavorable prognosis of the disease.[7]

HER2, a member of the EGFR family, is a membrane receptor protein that possesses tyrosine kinase activity and is expressed in various tumors such as breast cancer, gastric and gastroesophageal carcinoma, uterine serous carcinoma, and ovarian mucinous carcinoma. These findings support the beneficial effects of anti-HER2 monoclonal antibody therapy in managing these diseases. HER2 overexpression in cervical adenocarcinoma has been reported in a few studies, particularly in the gastric subtype. These studies have also revealed a correlation between this overexpression and advanced disease stages, in association with a worse prognosis.[8] Targeted therapy using the epidermal receptor breast B2 (ERBB2) and

ERBB3 genes, the coding genes for HER2 and HER3, is a new therapeutic approach for cervical adenocarcinoma that can potentially lead to hopeful outcomes. Consequently, in patients exhibiting HER2 mutation and amplification, targeted therapy using HER2 inhibition may help improve patient survival rates.[9,10,11] This study reveals the prevalence of HER2 expression in ENCA cases and considers the correlation between HER2 expression with clinicopathologic features, HPV infection status, SILVA pattern of invasion, disease prognosis, and patients' survival.

Materials and Methods

Data Collection

In this cohort study, data collection and review of pathology reports from 48 cases with the diagnosis of ENCA were done through an electronic search in the hospital information system (HIS) of the Pathology Department of the Cancer Institute of Imam Khomeini Hospital Complex (IKHC), Tehran, Iran, from 2016 to 2023. Two gynecologic pathologists reviewed all tumor slides of ENCA cases, including biopsy and surgical specimens, using a multi-headed microscope to select the proper paraffin blocks. All cases were assessed for HPV association status, histologic subtypes, SILVA pattern, stage, and metastasis or recurrence. Post-treatment patients' follow-up was obtained through access to medical records and making phone calls when necessary. The local Ethics Committee of the university approved this study (IR.TUMS.IKHC.REC.1401.105). Informed consent was obtained from the participants.

Histopathologic, Immunohistochemical and in situ hybridization assays

Based on the World Health Organization (WHO) recommendation, the morphological features were the main criterion for categorizing cases as HPV-associated or HPV-independent. The presence of abundant, easily identified mitosis and apoptosis on hematoxylin and eosin (H&E)-stained slides through low-power scanning magnification signified HPV-associated. Where morphological findings were not fully convincing, an immunohistochemistry study for evaluating p16 immunoreactivity was carried out to differentiate these two types. Diffuse staining (block type positivity) for p16 interpreted positive. All HPV-associated ENCA cases were categorized into three groups (SILVA-A, SILVA-B, and SILVA-C) based on the growth pattern of invasion mentioned in the WHO classification of female genital tumors, fifth edition (2020).[5]

After preparation of 3–4 µ-m unstained sections from the selected blocks, immunohistochemical staining for the HER2 marker was performed following the deparaffinization, retrieval steps, and subsequent incubation of the tissue sections with primary and secondary antibodies based on the kit instructions (Rabbit anti-human cytoplasmic epidermal Receptor Breast [c-erB2] monoclonal antibody, clone SP3, Master Diagnostica: Spain). HER2 expression was scored (0–3) according to the criteria for scoring HER2 expression in gastric and gastroesophageal adenocarcinomas and interpreted as 0 (negative), 1+ (negative), 2+ (equivocal), and 3+ (positive) (Table 1).[12]

A dual-probe fluorescence in situ hybridization (FISH) for HER2 and chromosome enumeration probe 17 (CEP17) was performed for equivocal cases to determine HER2 amplification. After hybridization, 20 interphase nuclei of cancer cells were observed for HER2 and CEP17 signals per nucleus through fluorescent microscopy and recorded as the ratio of total HER2 signals to CEP17 signals. HER2 amplification status (amplified or not) was finally interpreted according to the updated American Pathologist (ASCO/CAP) guideline for breast cancer (2018) (Table 2).[13]

Intra-tumoral heterogeneity for HER2 IHC staining is defined as a heterogeneous pattern-making staining spectrum with at least two score differences in the whole tumor section.

Ethics approval

This study adhered to the principles outlined in the Helsinki Declaration. The study was approved by the Ethics Committee of Tehran University of Medical Sciences (Approval number: IR. TUMS. IKHC. REC1401.105).

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) (IBM SPSS statistics version 27) and also statistical software for data science (STATA), version 17. The Chi square, Fischer exact test, independent sample t-test, and one-way Analysis of Variance (ANOVA) were used to determine the correlation of HER2 expression with histopathologic and clinical features and its analytical significance. The statistical threshold considered P value<0.05 (two-sided) as statistically significant.

Results

General characteristics

This study encompassed an evaluation of 48 cases of ENCA, including 35 (72.9%) HPV-associated and 13 (27.1%) HPV-independent instances. The mean age of the patients in the HPV-associated group was 46.60 ± 11.99 years, compared with 45.62 ± 15.40 years for HPV-independent patients, with no significant statistical difference (P = 0.81). Histological subtype distribution was observed as follows: Usual type (5 cases, 52.1%), gastric subtype (6 cases, 12.5%), ISMIC (6 cases, 12.5%), clear cell carcinoma (3 cases, 6.3%), adeno-squamous (3 cases, 6.3%), mesonephric (2 cases, 4.2%), adenocarcinoma, NOS (2 cases, 4.2%), and mucinous subtype (1 case, 2.1%) (Figure 1). The SILVA pattern was determined for 35 HPV-associated cases, including SILVA-A (1 case, 2.1%), SILVA-B (5 cases, 10.4%), and SILVA-C (29 cases, 60.4%). In the group of 22 cases (53.7%) with the usual subtype, 19 (86.3%) manifested at stage 1, while the remaining 3 (13.7%) were recognized at stage 2. Among the 5 cases of ISMIC with available data, 3 (60%) were in stage 1 and 2 (40%) in stage 3, which was significantly higher than other types of ENCA (P < 0.05). Between 5 cases (12.2%) of the gastric subtype, 3 (60%) were categorized as stage 4, 1 (20%) as stage 3, and 1 (20%) as stage 1. The other clinicopathologic features of study population including lymphovascular space invasion (LVSI), lymph node metastasis (LNM), rate of death and recurrence or metastasis are presented in table 3.

HER2 status

Assessment of 48 cervical adenocarcinoma samples revealed 8 (16.6%) HER2 positive instances, comprising 6 cases with a score of 3+ (positive) and 2 cases with a score of 2+ (equivocal) (Figure 2), which was amplified after the Fluorescence In Situ Hybridization (FISH) study (both with HER2/CEP ratio ≥2) (Figure 3). Totally, 40 (83.3%) cases were HER2 negative, including 10 cases with a score of 2+ (equivocal) and 30 with a score of 0 and 1 (negative) (Table 4) (Figure 2, 3).

All eight HER2-positive cases were found to be HPV-associated. In contrast, out of the 40 HER2 negative cases, 27 (67.5%) were HPV-associated, while the remaining 13 (32.5%) were HPV-independent (P = 0.08). Among 8 HER2-positive cases, 5 had the usual subtype and 3 were ISMIC (P = 0.45). More expression of HER2 in the ISMIC subtype (3 out of 6 cases: 50%) compared with the other histological subtype was statistically significant (P = 0.015) (Table 5).

There was intra-tumor heterogeneity for HER2 expression in 18 out of 48 cases (37.5%) of ENCA with scores of 2–3.

In our investigation, no statistically significant association was identified between HER2 expression and disease stage,

metastasis, LVSI, LNM, or SILVA pattern ($P > 0.05$) (Table 6).

No deaths, recurrence or metastasis were happened among HER2-positive patients. Conversely, all 13 deaths occurred within the HER2-negative group ($P > 0.05$).

Discussion

The findings of this study showed that 16.6% of ENCAs overexpressed HER2, with more IHC3+ cases. None of the evaluated cases were HPV-independent. HER2 overexpressed was found in half of the invasive stratified mucin-producing carcinomas (ISMICs). HER2 overexpression was not associated with stage, metastasis, LVSI, LNM, or SILVA pattern of invasion.

Given the increasing prevalence of cervical adenocarcinoma and worse prognosis compared with cervical SCCs, along with being more resistant to chemo-radiotherapy, identifying novel diagnostic markers and new therapeutic targets is needed to improve the disease prognosis.[14–17] Various biomarkers for targeted therapy have been proposed over the past decades. Anti-HER2 therapy has emerged as one of the most successful approaches, having received Food and Drug Administration (FDA) approval for the treatment of breast cancer, gastric cancer, and gastro-esophageal carcinoma characterized by HER2 overexpression.[18–19]

In gynecologic cancers, routine investigation of HER2 expression is well-established and recommended by the College of American Pathologists (CAP) for endometrial serous carcinoma. In other gynaecological cancers, including ENCA, it is less investigated. The prevalence of HER2 overexpression has been reported at 1%-21% in cervical cancers, particularly SCCs in previous studies.[20]

Fewer studies have demonstrated HER2 overexpression in cervical adenocarcinomas, with a broad range between 2.1% and 17.2% in recent studies, according to different study designs and methodologies.[21-23]

In our study, the HER2-positive prevalence rate (IHC 3+ and IHC 2+ amplified genes) was 16.6%, and all HER2-positive cases were from the HPV-associated group ($P = 0.08$). HER2-positive cases had the usual histological subtype and ISMIC. There was notable HER2 overexpression within the ISMIC subtype cases compared with the other subtypes ($P = 0.015$). However, other similar studies, such as Ayano Nakamura's study, have demonstrated HER2 expression predominantly in the gastric subtype of ENCA.[24]

We did not observe a significant correlation between HER2 expression and variables such as stage, metastasis, death, and overall survival ($P > 0.05$). However, the same studies revealed that HER2 expression had an association with advanced disease stage, increased metastasis, high mortality rates, and low overall survival. Halle et al. reported the prevalence of 30% HER2 overexpression and no correlation with poor clinical outcomes.[25]

The study conducted by Su Wang et al. reported the prevalence of HER2 overexpression in 17.2% of the cases. Furthermore, they found that HER2 overexpression was associated with a poor prognosis.[21] The study by Asako et al. showed that the co-expression of HER2 and EGFR significantly decreased the overall survival of patients with cervical adenocarcinoma.[14]

Haiyan Shi et al. conducted the most recent and the largest cohort, investigating 209 cases of cervical adenocarcinomas. They used the criteria as gastric adenocarcinoma for scoring of HER2 expression on IHC study as they found frequent “U-shaped” or lateral/ basolateral pattern of expression as well as intratumoral heterogeneity in their cases. The overall prevalence of HER2 expression among cervical adenocarcinoma in their patients was 12.4%. Gastric type adenocarcinoma (5/34: 14.7%) and HPV-

associated mucinous carcinoma (3/20: 15%) and usual adenocarcinoma (12/111: 10.8%) were the most common subtypes with HER2 overexpression. None of the 10 cases of ISMIC in their study were HER2-positive. They also mentioned that HER2 expression is associated with advanced disease stage, perineural invasion, and ovarian involvement.[22] No statistically significant difference was found between the frequency of HER2 overexpression in HPV-associated and HPV-independent adenocarcinoma, SILVA pattern of invasion and patient's age. Moreover, on survival analysis, HER2 overexpression was not an indicator for adverse clinical outcomes in their patients.[22] Abada et al. demonstrated that increasing FIGO stage among patients with cervical adenocarcinoma correlated with low HER2 expression and increased EGFR membranous staining, which lead to low patient survival rates.[26]

The differences between the study results may be related to several factors, such as sample size variation, low prevalence rate of cervical adenocarcinoma, and limitations in the statistical population. Technical issues, including tissue fixation, tissue processing protocols, variations in the HER2 antibodies used for IHC, and differences in IHC staining protocols and scoring methods, can also influence the results. Furthermore, the use of varying guidelines for interpretation of the HER2 IHC results and inter-observer variability for interpretation are determinative factors leading to different outcomes. Genetic diversity among the study populations should be considered as a possible factor contributing to different findings. Although our study had a smaller sample size, we used the same scoring method as the study conducted by Shi et al. Moreover, while gastric adenocarcinoma was frequently associated with HER2 overexpression, HPV-associated mucinous carcinomas were frequently positive for HER2 in their study. Unfortunately, we had only six cases of gastric adenocarcinoma, and all of them were negative for HER2. The small number of our cases in this group may affect our results.

In our study, three out of six cases of ISMIC revealed HER2 overexpression. ISMIC is a recently described HPV-associated subtype of ENCA with distinct morphology, immunohistochemical, and genetic alterations compared with SCC and the usual type of ENCA. They suggested that they originated from reserve cells and were more frequently associated with LVSI, LNM, higher stages, and worse clinical outcomes.[27] In our study, 40% of the cases with this diagnosis were in stage 3, significantly higher than the usual and other subtypes of HPV-associated adenocarcinomas (P = 0.004). High expression of HER2 in these cases and other subtypes of mucinous ENCAs can be investigated in future large-scale studies as a potential biomarker for targeted therapies.

Due to the absence of mortality among HER2-positive patients, survival analysis was not possible. The main limitation of our study is the constrained sample size and the limited number of cases within each histological subtype, which arise from the low prevalence rate of cervical adenocarcinoma. However, conducting multicenter studies can help overcome this issue to some extent.

Conclusion

ENCAs, including HPV-associated subtype, overexpress HER2 in about 16.6% of the cases. Overexpression in Invasive SMILE is significantly higher than the other subtypes, which can be considered for therapeutic trials in this histologic subcategory.

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Authors' Contribution

N. M: data gathering, analysis, interpretation, drafting the manuscript. F. N: study design, data gathering, analysis, interpretation, drafting and review. F. A, S.S, E. M, F. MS, N. Z: data gathering, reviewing the manuscript. All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of interest

None declared.

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Table 1. HER2 scoring based on 2017 ASCO/CAP criteria by IHC in Gastric and gastroesophageal junction adenocarcinoma

HER2 IHC Score	HER2 IHC Pattern in Surgical Specimen	HER2 Expression Assessment
0	No reactivity or membranous reactivity in < 10% of cancer cells	Negative
1+	Faint or barely perceptible membranous reactivity in > 10% of cancer cells; cells are reactive only in part of their membrane	Negative
2+	Weak to moderate complete, basolateral or lateral membranous reactivity in ≥ 10% of tumor cells	Equivocal
3+	Strong complete, basolateral or lateral membranous reactivity in ≥10% of cancer cells	Positive

ASCO/CAP: American Society of Clinical Oncology/College of American Pathologists; IHC: Immunohistochemistry; HER2: Human epidermal growth factor receptor 2

Table 2. The result of HER2 testing by in situ hybridization (dual probe assay)

Result	Criteria (dual-probe assay)
Negative	HER2/CEP17 ratio <2.0; <4.0 HER2 signals/cell
Negative	HER2/CEP17 ratio ≥2.0; <4 HER2 signals/cell and concurrent IHC 0-1+ or 2+ HER2/CEP17 ratio <2.0; ≥6.0 HER2 signals/cell and concurrent IHC 0-1+ HER2/CEP17 ratio <2.0; ≥4.0 and <6 HER2 signals/cell and concurrent IHC 0-1+ or 2+
Positive	HER2/CEP17 ratio ≥2.0; <4 HER2 signals/cell and concurrent IHC 3+ HER2/CEP17 ratio <2.0; ≥6.0 HER2 signals/cell and concurrent IHC 2+ or 3+ HER2/CEP17 ratio <2.0; ≥4.0 and <6 HER2 signals/cell and concurrent IHC 3+

IHC: Immunohistochemistry; HER2: Human epidermal growth factor receptor 2; CEP: Chromosome 17 centromere

Table 3. Clinicopathologic description and histopathologic subtypes of endocervical adenocarcinoma in the study population

Characteristics	Number
Total number of cases	
HPV associated	35 (72.9%)
HPV independent	13 (27.1%)
Age (mean ± SD)	
HPV associated	46.6 ± 11.9
HPV independent	45.6 ± 15.4
Sample type	
Biopsy	14 (29.2%)
Resection	34 (70.8%)
Histologic subtypes	
HPV-associated	
Usual	25 (52.1%)
Mucinous, NOS	1 (2.1%)
ISMIC	6 (12.5%)
Adenosquamous	3 (6.3%)
HPV-independent	
Gastric	6 (12.5%)
Clear cell	3 (6.3%)
Mesonephric	2 (4.2%)
NOS	2 (4.2%)
Stage	
1	29 (60.4%)
2	5 (10.4%)
3	3 (6.3%)
4	4 (8.3%)
SILVA pattern	
A	1 (2.1%)
B	5 (10.4%)
C	29 (60.4%)
LVSI	
Yes	27 (56.3%)
No	10 (20.8%)
LNM	
Yes	8 (16.7%)
No	29 (60.4%)
Metastasis	
Yes	11 (22.9%)
No	21 (43.8%)

HPV: Human papilloma virus; NOS: Not otherwise specified; ISMIC: Invasive stratified mucinous carcinoma; LVSI: Lymph-vascular space invasion; LNM: Lymph node metastasis

Table 4. HER2 status in study population

	Number
HER2 score	
0,1	30 (62.5%)
2	12 (25%)
3	6 (12.5%)
FISH study on equivocal results	
Amplified	2 (ratio>2)
Not amplified	10
Final HER2 results	
Positive	8 (16.66%)
Negative	40 (23.33%)

HER2: Human epidermal growth factor receptor 2; FISH: Fluorescent in situ hybridization

Table 5. HER2 status and distribution in different histological subtypes

Histologic subtype	HER2 positive	HER2 negative
HPV associated	8 (22.85%)	27 (77.14%)
Usual	5 (20%)	20 (20%)
ISMIC	3 (50%)	3 (50%)
Mucinous	0	1 (100%)
Adenosquamous	0	3 (100%)
HPV independent	0	13 (100%)
Gastric	0	6 (100%)
Clear cell	0	3 (100%)
Mesonephric	0	2 (100%)
NOS	0	2 (100%)

HPV: Human papilloma virus; ISMIC: Invasive stratified mucinous carcinoma; NOS: Not otherwise specified

Table 6. Association of HER2 status with clinicopathologic features

Clinicopathologic features	HER2 positive	HER2 negative	*P* value
Age (mean ± SD)	43.5 ± 9.8	46.9 ± 13.3	0.50
HPV status			
HPV associated	8 (22.9%)	27 (77.1%)	0.08
HPV independent	0	13 (100%)	
Stage			
1	6 (20.7%)	23 (79.3%)	0.55
2	0	5 (100%)	
3	1 (33.3%)	2 (66.7%)	
LVSI			
Yes	4 (14.8%)	23 (85.2%)	0.65
No	2 (20%)	8 (80%)	
LNM			
Yes	2 (25%)	6 (75%)	0.59
No	4 (13.8%)	25 (86.2%)	
Silva pattern			
A	0	1 (100%)	0.54
B	2 (40%)	3 (60%)	
C	6 (20.7%)	23 (79.3%)	
Metastasis			
Yes	0	11 (100%)	0.13
No	5 (23.8%)	16 (76.2%)	
Patient's survival			
Alive	8 (100%)	26 (66.7%)	0.08
Dead	0	13 (33.3%)	

HPV: Human papilloma virus; LVSI: Lymph-vascular space invasion; LNM: Lymph node metastasis

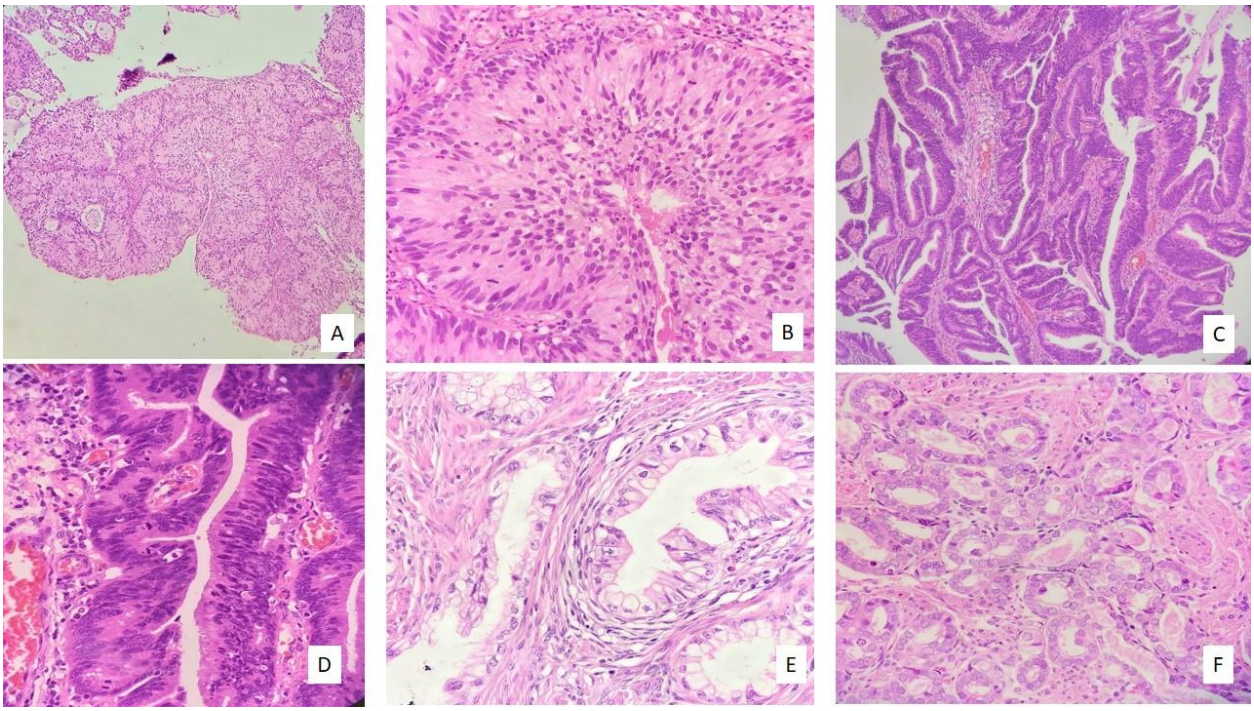

Figure 1. Histopathological features of different subtypes of endocervical adenocarcinomas are shown. A, B) stratified squamous epithelium with full thickness distribution of mucinous cells is seen (Invasive stratified mucin producing adenocarcinoma) (100×, 400×) (C, D) Usual subtype of HPV-associated endocervical adenocarcinoma is composed of glandular structures with columnar pseudostratified epithelial lining. (100×, 400×). Easily identifiable mitosis and apoptosis are characteristic. E) Gastric type of HPV-independent endocervical adenocarcinoma is seen which shows glandular structures with columnar cells containing pale cytoplasm, distinct cell borders and low mitosis (400×). F) Mesonephric subtype of HPV-independent endocervical adenocarcinoma shows small tubular structures containing eosinophilic material. (400×).

HPV: Human papilloma virus

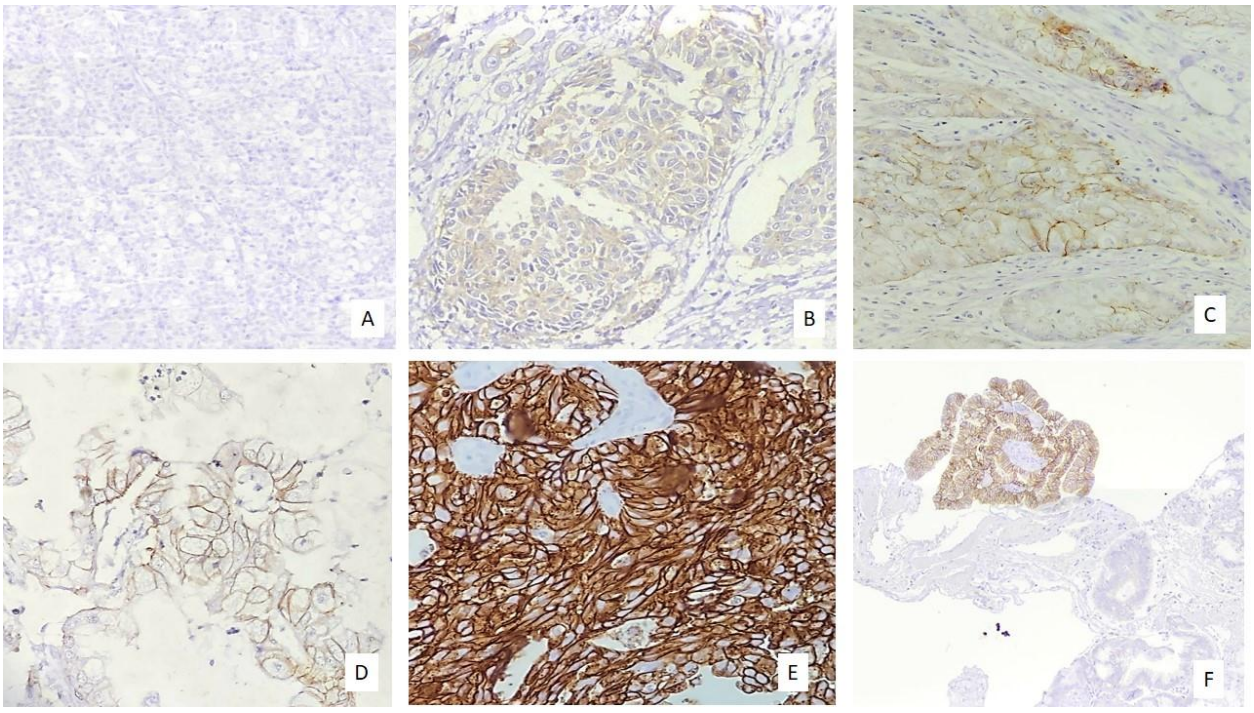

Figure 2. HER2 expression on IHC study using the ASCO/CAP protocol for gastric adenocarcinomas which shows: A) Negative staining (score 0), B) Negative (score 1, faint staining in >10% of tumor cells), C) Equivocal (score 2 weak staining in > 10% tumor cells, D) Equivocal (score 2, moderate reactivity in > 10% tumor cells, E) Positive (score 3, strong staining in >10% of tumor cells), F) Heterogeneous staining showing more than 2+ staining difference in different population of tumor cells.

HER2: Human epidermal growth factor receptor 2; IHC: Immunohistochemistry; ASCO/CAP: American Society of Clinical Oncology/College of American Pathologists

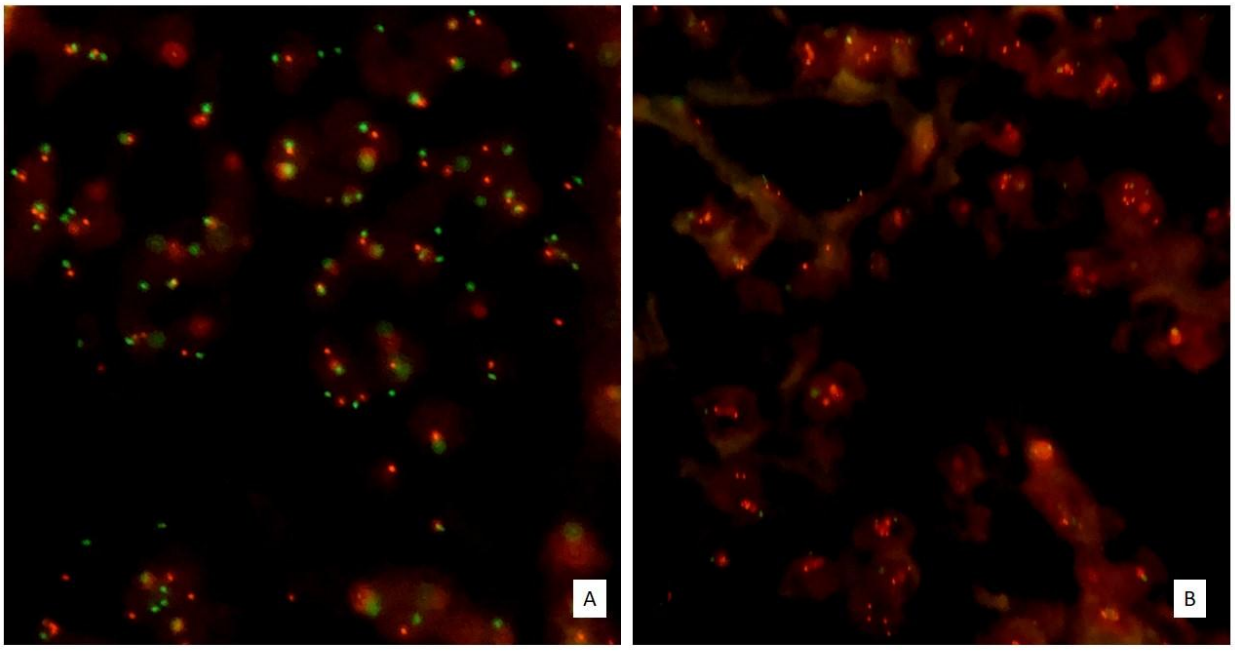

Figure 3. Fluorescent in situ hybridization study shows A) Negative result (HER2/CEP ratio ≤2) and B) HER2 amplification (HER2/CEP ratio ≥2)
HER2: Human epidermal growth factor receptor 2; CEP: Chromosome 17 centromere