

Clinicopathological features and outcomes in different histologic subtypes of HPV-independent endocervical adenocarcinomas

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Abstract

Background: We aim to analyze the clinicopathological features and outcomes among different histologic subtypes of HPV-independent endocervical adenocarcinomas (HPVI ECAs).

Methods: Forty-five HPVI ECAs, including 16 minimal deviation adenocarcinoma (MDA), 17 non-MDA type of gastric adenocarcinoma (GAS), and 12 non-GAS HPVI ECAs were studied. Data of clinical features, pathological characteristics, treatment, and outcomes were evaluated.

Results: The median age of patients with GAS was 46 years old (IQR: 41.5, 59.5), with no significant difference compared to patients with non-GAS HPVI ECA (48-year-old, IQR: 40.5, 60.5) ($p=0.92$). Compared with non-GAS HPVI ECAs, GAS had more common complains of vaginal watery discharge ($p=0.047$). GAS cases were also associated with higher clinical stage at diagnosis ($P=0.016$), deeper cervical stromal invasion ($p=0.01$), and worse 5-year progression free survival (PFS) ($p=0.032$). Compared with non-MDA GAS, MDA had similar clinical and pathological features and prognosis. Of note, cytology results showed a lower positivity rate for HPVI ECAs (65.2% for GAS and 60% for non-GAS HPVI ECA), and MDA had a lower positivity rate than that for non-MDA (40.0% vs 84.6%, $p=0.026$). Serum CA19-9 levels were significantly higher in MDA than those in non-MDA (184.5 U/ml vs 22.4U/ml, $p=0.045$) and non-GAS cases (184.5U/ml vs 10.6U/ml, $p=0.006$).

Conclusions: GAS HPVI ECA had different clinical presentation with genital watery discharge compared with non-GAS HPVI ECA cases. Comparison with those of non-GAS HPVI ECAs, GAS cases were more likely to have high risk pathological factors and poorer PFS. Serum CA19-9 may be helpful for diagnosis and screening in patients with GAS, especially those with MDA.

Background

Endocervical adenocarcinomas (ECAs) comprise up to 25% of all cervical cancers(1–3), and are frequently related to persistent infection of human papillomavirus (HPV) 16/18/45(4). There is also a small subtype of non-HPV-associated ECAs(1, 3, 5, 6). Unlike HPV-associated ECAs, non-HPV-associated ECAs are frequently located in the upper endocervix, resulting in missed detection or misdiagnosis(7, 8). According to the 2020 World Health Organization (WHO) Classification of Female Genital Tumors(9), ECAs are subclassified into HPV-associated (HPVA) and HPV-independent (HPVI) groups. HPVI ECAs include gastric type ECA (GAS) [including minimal deviation adenocarcinoma (MDA)], endometrioid carcinoma (EMCA), clear cell adenocarcinoma (CCC), serous carcinoma, mesonephric carcinoma (MC), and adenocarcinoma, not otherwise specified (NOS). First described by Japanese groups(10–12), GAS, including MDA, is the second most common subtype of ECA and the most common subtype of HPVI ECAs(13). Although considered rare in Western countries(14, 15), GAS accounts for up to 25% of all ECAs in Asian population(11, 16). Other types of HPVI ECAs are rare, and data about their clinical behavior is limited.

HPVI ECAs are frequently present with an advanced stage and poor prognosis. However, the clinical features and prognosis may differ among different histological subtypes of HPVI ECAs(11, 15). Currently, large clinicopathologic studies in this field are limited. Here, we conduct a relatively large retrospective analysis focused on the clinicopathological features and outcome of different subtypes HPVI ECAs to provide a useful reference for the diagnosis and treatment of such tumors.

Methods

Case selection

Patients with a final diagnosis of HPVI ECAs from 2014 to 2020 in our hospital were identified. Hematoxylin and eosin (H&E) and immunohistochemical (IHC) staining slides were reviewed by 2 gynecologic pathologists (F. Zhou and XF. Zhang) in a blinded fashion and the pathologic diagnosis was confirmed. All related clinical data including age, symptoms, imaging materials, level of serum CA19-9, treatment, clinical outcome were collected from the electronic clinical information system database. All tumors were classified according to the 2020 WHO Classification of Female Genital Tumors. Patients were clinically staged using the 2018 International Federation of Gynecology and Obstetrics (FIGO) system. The results of thinprep cytologic test (TCT), high-risk HPV (hrHPV) (tested by Aptima, Cervista or hybrid capture 2 assay), and p16 performed as part of clinical care were recorded. Informed consent was obtained from all subjects involved in the study. IRB approval was obtained by the Ethics Committee of our hospital.

Serum CA19-9 examination

Serum CA19-9 was estimated by using an automated chemiluminescence analyzer (Shanghai Roche Diagnostic products Co., LTD., China). All assay procedures were performed based on manufacturer instructions. The normal upper limitation is 39U/ml.

Statistical Analysis

Abnormally distributed parametric variables were compared by the Mann–Whitney U-test. Comparison of categorical data was performed by Chi's test. The Kaplan-Meier method was used to generate survival curves. The log-rank test was employed to compare the survival curves. Progression-free survival (PFS) was calculated from the date of diagnosis to the date of tumor recurrence, progression, or death. The overall survival (OS) was defined as the time between the date of surgery and the last date of follow-up or death from any cause. All statistical analyses were performed with the IBM SPSS statistical software, version 20.0. Two-sided P values were reported. P values less than 0.05 were considered statistically significant.

Results

Clinicopathological features of HPVI ECA.

From 2014 to 2020, totally 502 cases were diagnosed with ECA or ECA in situ. Forty-five cases (9.0%) were confirmed as HPVI ECA. The specimens of HPVI ECA included 38 hysterectomies, 2 cone excisions, and 5 biopsies. Among them, 33 cases were GAS (including 16 MDA) and 12 were non-GAS HPVI ECAs (including 8 CCC, 3 EMCA, and 1 MC, Fig. 1). 45 of 45 (100 %) HPVI ECAs were p16 negative or patchy positive. hrHPV test results were available for 39 of 45 (86.7%) HPVI ECAs, all of which were negative. The rest of 6 HPVI ECAs (3 GAS and 3 CCC) had no records of hrHPV testing but with negative or patchy positive of p16. Patient pathologic diagnosis, p16 status, and HPV status information are summarized in Table S1.

Comparison of clinical features between GAS and non-GAS HPVI ECA

The median age of patients with GAS was 46 years old (IQR: 41.5, 59.5), with no significant difference compared with that of patients with non-GAS HPVI ECA (48 years, IQR: 40.5, 60.5, $p = 0.92$). 24 patients with GAS had clinical symptoms, with 16/24 (66.7%) complained of irregular bleeding or contact bleeding and 8/24 (33.3%) experienced vaginal watery discharge. Meanwhile, 9 patients with non-GAS HPVI ECAs had clinical symptoms, in which all 9/9 (100%) patients had irregular vaginal bleeding or contact bleeding. Vaginal watery discharge was more frequently noted in GAS cases than in non-GAS HPVI ECAs ($p = 0.047$). Combined pelvic examination with imaging data, although there was no significant difference in lesion size of the greatest dimension between the two groups, 14 patients (42.4%) in the GAS group had a tumor size larger than 4 cm, while only 2 patients (16.7%) in the non-GAS group had a tumor size larger than 4 cm ($p = 0.11$). Seen Table 1.

Table 1

Comparing of clinical features between gastric-type and non-gastric type cervical adenocarcinoma.

Clinical features	GAS	Non-GAS	P value
Age (median, IQR)	46 (41.5,59.5)	48 (40.5,60.5)	0.92
Symptoms (n, %)			0.047
Bleeding	16 (63.6%)	9 (100%)	
Watery discharge	8 (36.4%)	0 (0%)	
Tumor Size in the largest dimension (n, %)			0.11
< 4cm	19 (61.3%)	10 (83.3%)	
≥ 4cm	14 (38.7%)	2 (16.7%)	
TCT (n, %)			0.83
NILM	8 (28.6%)	2 (40%)	
Abnormal	15 (71.4%)	3 (60%)	
Stage (n, %)			0.016
I-IIA	14 (46.7%)	8 (88.9%)	
IIB-IV	18 (53.3%)	1 (11.1%)	
Lymph nodes metastasis (n, %)			0.06
Negative	20(70.4%)	9(100%)	
Positive	9 (29.6%)	0(0%)	
Deep stromal invasive (n, %)			0.01
Negative	4(14.2%)	5(55.6%)	
Positive	25 (85.2%)	4 (44.4%)	
LVSI (n, %)			0.13
Negative	18(63.0%)	8(88.9%)	
Positive	11 (37.0%)	1 (11.1%)	

Twenty-three of GAS cases had TCT results, with 8/21 (34.8%) were negative for intraepithelial lesions or malignancy (NILM). Five non-GAS HPVI ECAs had TCT results, with 2/5 (40%) were NILM. There was no difference in positivity rate of TCT between GAS (65.2%) and non-GAS type (60%, p = 0.83). Seen Table 1. **Comparison of pathological risk factors and staging between GAS and non-GAS HPVI ECA**

In total, 38 hysterectomies (29 GAS and 9 non-GAS HPVI ECAs) were available for analyzing ancillary factors. The incidence of lymph nodes metastasis and lymphovascular space invasion (LVSI) in GAS (31.0% and 37.9%, respectively) was higher than that of non-GAS HPVI ECAs (0% and 11.1%, respectively), although there was no statistically significant difference ($p = 0.06$ and $p = 0.14$, respectively). The incidence of deep stromal invasion in GAS was significantly higher than that in non-GAS HPVI ECAs (86.2% vs 44.4%, $p = 0.01$) (Table 1).

Among the 41 HPVI ECAs (32 GAS and 9 non-GAS HPVI ECAs) with clinical pathological staging information, 14/32 (43.8%) were staged as I-IIA and 18/32 (56.2%) were staged as IIB-IV for GAS. Meanwhile, for non-GAS HPVI ECAs, 8/9 (89%) were staged I-IIA and 1/9 (11%) was staged IIB-IV. Here we used IIA as the boundary to state which type of HPVI ECA is more likely to infiltrate into the parametrial, pelvic cavity or have distant metastasis. Patients with GAS were more likely to have an advanced clinical stage by infiltration into parametrial and remote organs compared with those of non-GAS HPVI ECAs ($p = 0.016$).

Comparison of outcome between GAS and non-GAS HPVI ECA

In GAS, 31 of 33 patients underwent surgery. Except for one patient who underwent a radical trachelectomy, the remaining 30 were all treated with radical hysterectomy and lymphadenectomy. 27/33 (81.8%) received radiotherapy (RT)/chemotherapy (CT) as post-operative adjuvant treatment. Meanwhile, 4/33 (12.1%) received surgery only. 2/33 (6.1%) received concurrent chemo-radiotherapy without surgery. In non-GAS HPVI ECAs, 11 of 12 patients received radical hysterectomy with pelvic lymphadenectomy. Of the patients with surgical management, 10/11 of these cases received adjuvant RT/CT. 1/12 (8.3%) received RT and CT without operation (Table S2).

Complete follow-up information was available and included in a survival analysis for 45 patients with HPVI ECA. In the GAS group, 8 patients relapsed, with lesions in the pelvic cavity, vaginal stump, great omentum metastasis, intestinal metastasis, pulmonary metastasis, etc. A total of 5 patients died. In the non-GAS group, there was no recurrence or death until the last follow-up. The 5-year PFS and OS rate of patients in GAS group were 63.0% and 74.0%, respectively. The rates in non-GAS group were both 100%. There was a significant difference in 5-year PFS ($p = 0.033$) and no difference in OS ($p = 0.079$) between the two groups. (Fig. 2 & Table S2)

Comparison of clinicopathological features and outcomes between MDA and non-MDA

In GAS cases, 16/33 (48.4%) were diagnosed as MDA and 17/33 (51.6%) were diagnosed as non-MDA GAS. There were no statistical differences between the two groups in age ($p = 0.37$), symptoms ($p = 0.15$), and tumor sizes ($p = 0.37$). Only the cytological results of TCT were significantly different, with NILM result more common in MDA group than that in non-MDA group (60.0% vs 15.4%, $P = 0.026$). Additional histologic risk factors were also evaluated, including lymph node metastasis ($p = 0.78$), deep stromal invasion ($p = 0.24$), and LVSI ($p = 0.32$) were all similar between MDA and non-MDA GAS. (Table 2). A total of 3 cases reoccurred and 1 case died during the follow-up in MDA patients. In non-MDA patients, 5

cases reoccurred, and 4 cases died. There was no significant difference of survival outcomes of 5-year PFS (71.0% vs 59.0%, $p = 0.328$) and 5-year OS (89.0% vs 59.0%, $p = 0.09$) between two groups. (Fig. 3)

Table 2
Comparison of Clinical features between MDA and non-MDA GAS.

Clinical features	MDA	Non-MDA	P value
Age (median, IQR)	46 (43.5, 62)	43 (38.5, 58)	0.37
Symptoms (n, %)			0.15
Bleeding	7 (53.8%)	9 (81.8%)	
discharge	6 (46.2%)	2 (18.2%)	
Tumor Size in the greatest dimension (n, %)			0.37
< 4cm	8 (50.0%)	11 (64.7%)	
≥ 4cm	8 (50.0%)	6 (35.3%)	
TCT (n, %)			0.026
NILM	6 (60.0%)	2 (15.4%)	
Abnormal	4 (40.0%)	11 (84.6%)	
Stage (n, %)			0.47
I-IIA	8 (50.0%)	6 (37.5%)	
IIB-IV	8 (50.0%)	10 (62.5%)	
Lymph node metastasis (n, %)			0.78
Negative	10(71.4%)	10(66.7%)	
Positive	4 (28.6%)	5 (33.3%)	
Deep stromal invasive (n, %)			0.24
Negative	3 (21.4%)	1(6.7%)	
positive	11 (78.6%)	14 (93.3%)	

Comparison of CA19-9 among MDA, non-MDA, and non-GAS HPVI ECA

We compared the level of serum CA19-9 among MDA, non-MDA, and non-GAS types. The median level of CA199 was 184.5U/ml (IQR:48.8,415.4) in MDA type, 22.4U/ml (IQR:12.5-182.9) in non-MDA type, and 10.6 U/ml (IQR: 6.3, 59.8) in non-GAS type. Compared with the non-MDA group, the level of CA199 in MDA type was significantly higher, $p = 0.045$. Compared with the non-GAS group, the level of in MDA type was also significantly higher, $p = 0.006$. No significant difference was found between group of non-MDA and

non-GAS, $p = 0.128$. The number of patients with abnormal CA19-9 levels(> 39U/ml) in different groups was also analyzed. The cases with elevated CA19-9 were more in MDA group than that in the non-MDA group ($p = 0.009$) and non-GAS group ($p = 0.027$). Seen Table 3.

Table 3

Comparing of cases with different levels of serum CA199 among MDA, non-MDA and non-GAS

CA199	MDA (n, %)	non-MDA (n, %)	non-GAS (n, %)
< 39U/ml	4 (25.0%)	12 (70.6%)	8 (66.7%)
$\geq 39U/ml$	12 (75.0%)	5 (29.4%)	4 (33.3%)
P		0.009 [†]	0.027 [‡]

[†] Cases of MDA compared with non-MDA, [‡] Cases of MDA compared with non-GAS.

Discussion

This is a large retrospective study of HPVI ECAs, whose HPV independent activities were confirmed by clinicopathological characteristics including p16 and hrHPV results. In our study, GAS cases had a different constellation of clinical presentation and laboratory results compared with non-GAS HPVI ECA cases, including vaginal watery discharge and elevated serum CA19-9. In addition, GAS cases were more likely to have deep cervical stromal invasion and an advanced stage when compared against those of non-GAS HPVI ECAs. Finally, GAS cases were more commonly found to have poorer PFS.

In this series of HPVI ECA cases, GAS was the most common type, which accounted for 73.3% of all studied cases, followed by CCC (17.8%). The prevalence of different histologic types was similar to Stolnicu et al.'s report(13), in which they studied 40 cases of HPVI ECAs. Of those 40 cases, GAS and CCC accounted for 67.3% and 20%, respectively. Stolnicu et al.(13) reported patients with non-GAS HPVI ECA tended to be older. However, the ages of different subtypes of HPVI ECA were similar in other reports(17, 18). These discrepant results may be related to the limited number of cases of these studies. In our cohort, the ages of patients with GAS or non-GAS HPVI ECAs were similar, with the median age being 46 (IQR: 43.5, 62) in MDA, 43 (IQR: 38.5, 58) in non-MDA GAS, and 48 (IQR: 40.5, 60.5) in non-GAS HPVI ECAs.

Unlike usual type HPVA ECAs, GAS is frequently located in the upper endocervix and present with a bulky cervix(7, 8). Because the number of such cases is relatively limited, reports about the comparison of clinical characteristics, pathological features and outcomes between GAS and non-GAS HPVI ECA are rare(11, 15). According to our findings, the clinical manifestations of GAS included vaginal watery discharge and/or bleeding, while patients with non-GAS HPVI ECA mostly complained of vaginal bleeding. Consensus guidelines for management of cervical dysplasia in the screening setting have not yet been reached to accommodate the three most widely available screening strategies: primary HPV

testing, co-testing with HPV testing and cervical cytology, and cervical cytology alone(19). This is a critical need for these guidelines because HPVI ECAs are negative for hrHPV, and cytology results become more important especially in those without abnormal appearance of cervix. According to previous reports, the positivity rate of TCT screening in ECAs is 40–50%, which is much lower than that in SCCs (above 90%) (20). Nakamura et al.(21) reported 78% NILM of TCT were found in the GAS group. Our study indicated a similar result that TCT had a low positivity rate for HPVI ECAs (71.4% for GAS and 60% for non-GAS HPVI ECA). Thus, some of these cases may be missed during conventional screening because of negative results from both hrHPV and cytology. As a result, the patient with HPVI ECA is frequently diagnosed at a relatively later stage. Of note, the TCT results showed higher rate of NILM in MDA than the rate of NILM in non-MDA GAS (60.0% vs 15.4%, p = 0.026). This suggests that MDA is more prone to be missed and misdiagnosed clinically.

CA19-9 is of great clinical importance in the diagnosis, treatment and prognosis of gastrointestinal malignancies, and it is closely related to disease progression(22–24). However, elevated serum CA19-9 in ECAs has rarely been reported. Until now, only Nakamural et al.(21) reported that serum CA19-9 in GAS was higher than that in non-GAS HPVI ECAs. They compared the rate of cases with elevated CA19-9 levels, and found it was higher than the rate of levels among non-GAS HPVI ECAs. However, in their report, some cases with hrHPV infection were also included in the non-GAS HPVI ECAs. In our study, we found that the serum CA19-9 level of patients with MDA GAS was significantly higher than that of patients with non-GAS HPVI ECA (184.5 U/ml vs 10.6U/ml, p = 0.006). We also found that CA19-9 level was significantly higher in MDA than that in non-MDA GAS (184.5 U/ml vs 22.4U/ml, p = 0.045). And the number of cases with elevated serum CA19-9 was more in MDA than in both non-MDA and non-GAS (p = 0.009 and p = 0.027 respectively). It demonstrated that the elevated serum CA19-9 was mainly occurred in MDA ECAs. Thus, it might be an effective tumor marker for the differential diagnosis of MDA, and non-MDA or non-GAS. As mentioned before, MDA is more prone to be missed by cytology. Taken together, CA19-9 might be an effective tumor marker for clinical diagnosis of GAS, especially for MDA.

Kojima et al.(17) demonstrated higher frequencies of destructive invasive patterns, LVSI, and advanced stage in HPVI ECAs. We further analyzed the stage and pathological features of GAS and non-GAS HPVI ECAs. In our study, GAS cases were more likely to be in the stage above IIB than those of non-GAS HPVI ECAs (56.2% vs 11.1%, p = 0.016). Karamurzin et al.(15) reported that 59% of GAS were staged over II, which was a significant difference when compared with HPVA ECA cases. A previous report showed that GAS had always been diagnosed at a more advanced stage than usual type HPVA ECAs(11). According to our results, GAS cases were more likely to infiltrate into the parametrial and pelvic organs than non-GAS HPVI ECA cases. In addition, there were significant differences in presence of deep stromal invasion in GAS compared with non-GAS HPVI ECAs (86.2% vs 44.4%, p = 0.01). Although no significant difference was found in lymph nodes metastasis and LVSI between GAS and non-GAS HPVI ECAs, the incidence seems to be higher in GAS (31.0% vs 0% and 37.9% vs 11.1%, respectively).

It has been reported that HPVA ECAs portend better prognosis than HPVI ECAs, including OS, DFS, and PFS. Kojima et al.(11) demonstrated that patients with HPVI ECA (including 12 GAS and 4 MDA) had

significantly decreased 5-year DFS compared with usual type HPVA ECA. In addition, GAS was associated with an increased risk of recurrence compared with non-GAS HPVI ECA. Karamurzin et al.(15) reported that disease specific survival (DSS) at 5 years was 42% for GAS compared with 91% for usual type HPVA ECAs. Few studies have focused on outcomes of GAS and non-GAS HPVI ECAs. We found that the prognosis of GAS was worse than that of non-GAS HPVI ECAs. The recurrence rate (22.6% vs 0%) and mortality rate (18.0% vs 0%) were all higher in the GAS group. Moreover, there was a significant difference in 5-year PFS ($p = 0.033$) between GAS and non-GAS HPVI ECA cases. No statistical difference was found in OS ($p = 0.079$), mainly due to the limited number of non-GAS HPVI ECA. In our study, the most common postoperative adjuvant therapy was RT combined with CT for GAS, regardless of eligibility according to the SEDLIS criteria by NCCN. The value of adjuvant therapy after surgery needs further investigation.

There has been considerable debate about clinical outcomes of MDA since compared with HPVA ECA. Several studies had indicated its relatively aggressive nature(7). Nishio et al.(25) reported that more than half the patients died of disease, and only three patients were alive without recurrence after 2 years of follow-up. Karamurzin et al.(15) reported forty cases of GAS including 13 of MDA and 27 of non-MDA subtype and found no clinical and survival difference between MDA and non-MDA GAS. Similar to the results of Karamurzin et al, we found no differences between these two groups, including clinical complaints, tumor size, stage, lymph node metastasis, LVS_I, deep stromal invasion, and survival outcomes.

Conclusions

Screening for successful diagnosis is difficult for patients with HPVI ECA. GAS HPVI ECA had different clinical presentation with genital watery discharge compared with non-GAS HPVI ECA cases. Comparison with those of non-GAS HPVI ECAs, GAS cases were more likely to have high risk pathological factors such as lymph node metastasis and deep stromal invasion, and poorer PFS. Serum CA19-9 may be helpful for diagnosis and screening in patients with GAS, especially those with MDA.

Abbreviations

CCC: clear cell adenocarcinoma; CT: chemotherapy; ECAs: Endocervical adenocarcinomas; FIGO: International Federation of Gynecology and Obstetrics; GAS: gastric adenocarcinoma; HPV: human papillomavirus; HPVA: HPV-associated; HPVI: HPV-independent; HPVI ECAs: HPV-independent endocervical adenocarcinomas; H&E: Hematoxylin and eosin; hrHPV: high-risk HPV; IHC: immunohistochemical; LVS_I: lymphovascular space invasion; MC: mesonephric carcinoma; MDA: minimal deviation adenocarcinoma; NILM: negative for intraepithelial lesions or malignancy; NOS: not otherwise specified; OS: overall survival; PFS: progression free survival; RT: radiotherapy; TCT: thinprep cytologic test; WHO: World Health Organization

Declarations

Authors' contributions

Conceptualization, Weiguo Lu, Feng Zhou and Xiaoyun Wan; methodology, Lili Chen, Feng Zhou, and Xiaofei Zhang; investigation, Lili Chen, Yizhen Niu, Lina Yu, and Liya Dong; data curation, Lili Chen, and Zhou Feng; writing—original draft preparation, Lili Chen and Feng Zhou; writing—review and editing, Lili Chen and Amanda Louise Strickland; supervision, Weiguo Lu and Xiaoyun Wan; project administration, Lili Chen; funding acquisition, Weiguo Lu. All authors have read and agreed to the published version of the manuscript.

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Availability of data and materials

The data in the current study are not publicly available on account that data came from the medical records where sensitive information is collected, but anonymized information is available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of Zhejiang University School of Medicine Women's Hospital. Informed consent was obtained from all individual participants included in the study.

Consent for publication

Not Applicable.

Competing interests

The authors have declared that no competing interest exists.

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Figures

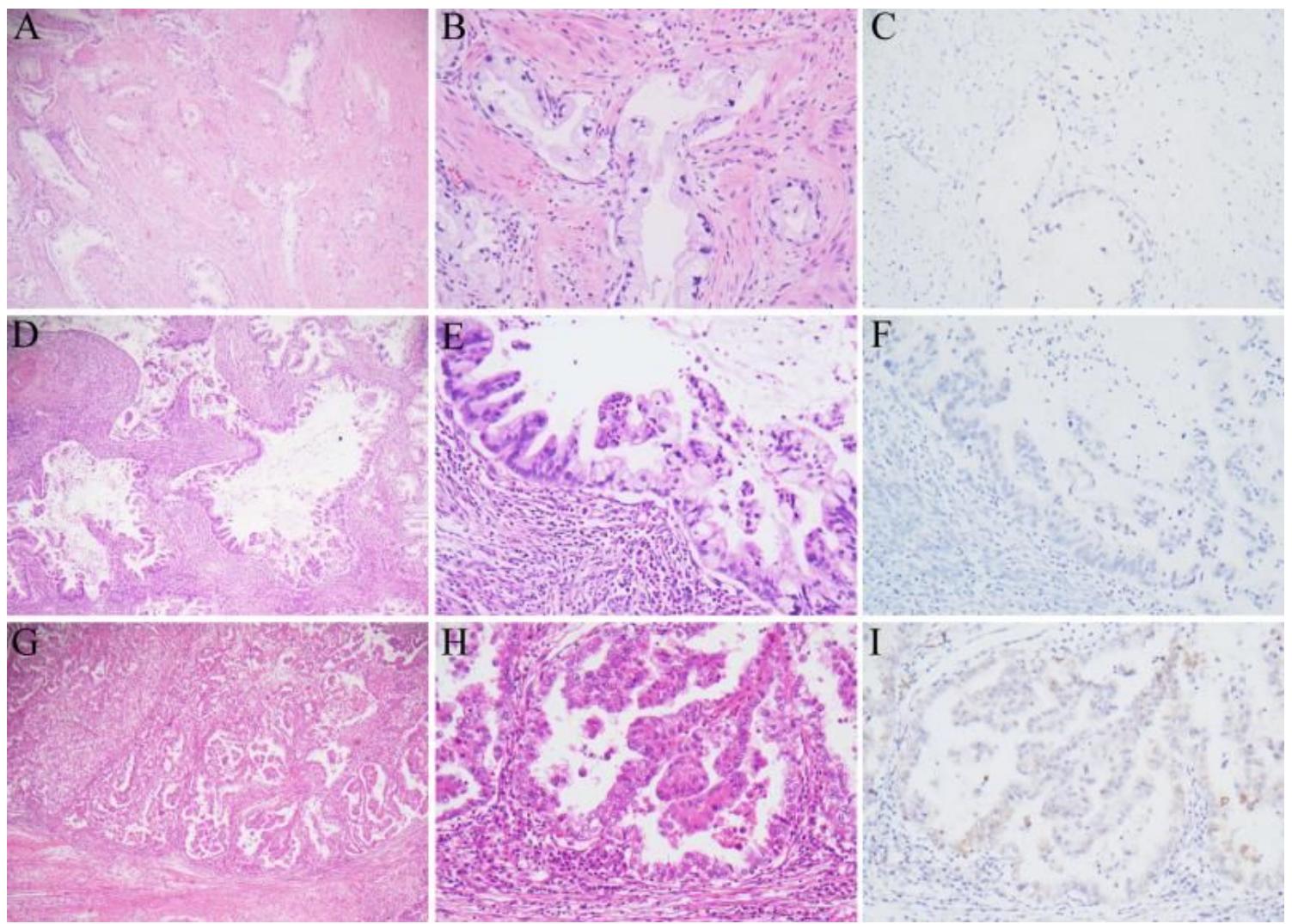


Figure 1

Examples of different histological types of HPV independent endocervical adenocarcinoma. (A-C) Minimal deviation adenocarcinoma (MDA): (A) Well-formed glands diffusely infiltrating cervical wall (H&E, 50 x). Neoplastic cells with clear and voluminous cytoplasm and basally located nuclei with mild cytologic atypia. (H&E, 200 x). (C) Negative p16 expression in tumor cells. (D-F): Moderately differentiated gastric type adenocarcinoma: (D) Papillary proliferation of non-MDA gastric type adenocarcinoma (H&E, 50 x). (E) Neoplastic cells with moderate cytologic atypia and abundant clear cytoplasm showing distinct cell borders (H&E, 200 x). (F) Negative p16 expression in tumor cells. (G-I) Clear cell carcinoma: (G) Neoplastic glands infiltrating fibromatous stroma (H&E, 50 x). (H) Tumor cells with clear cytoplasm and severe nuclear atypia (H&E, 200 x). (F) Patch p16 expression in tumor cells.

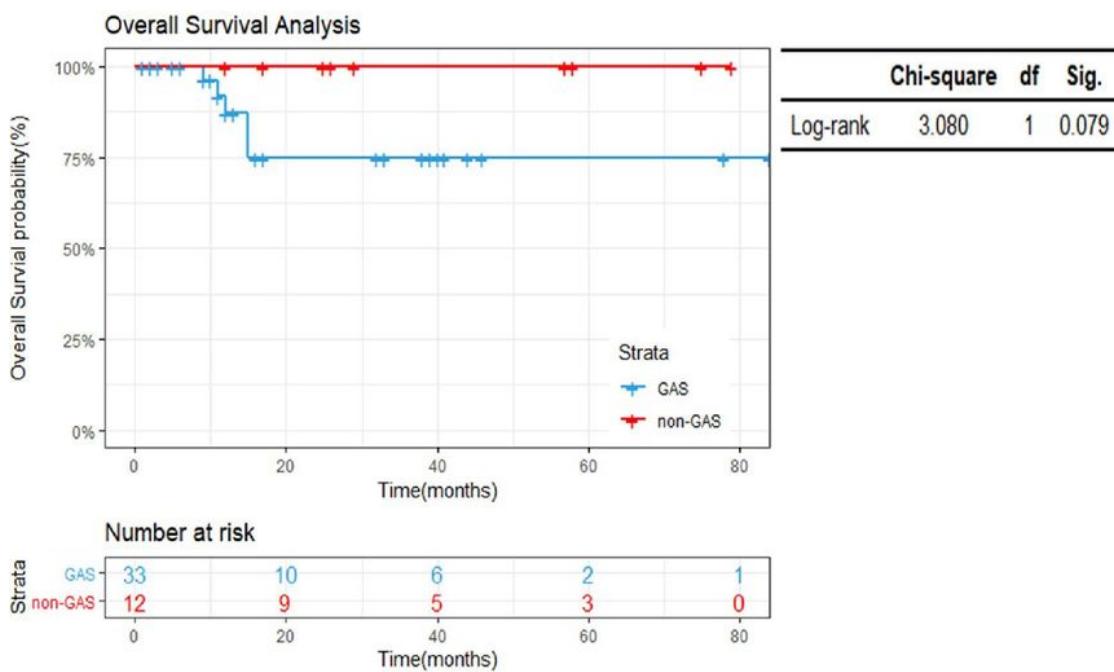
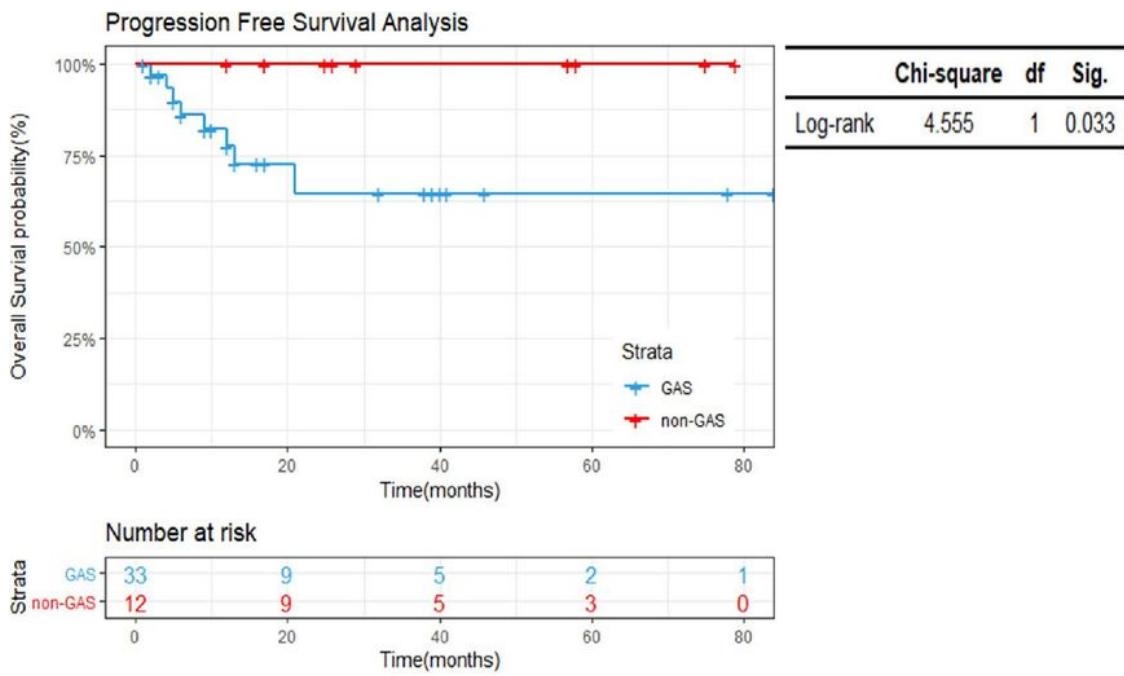


Figure 2

Kaplan-Meier progression free survival (PFS) and overall survival (OS) analysis for GAS vs. non-GAS. Abbreviations: GAS=gastric type ECA.

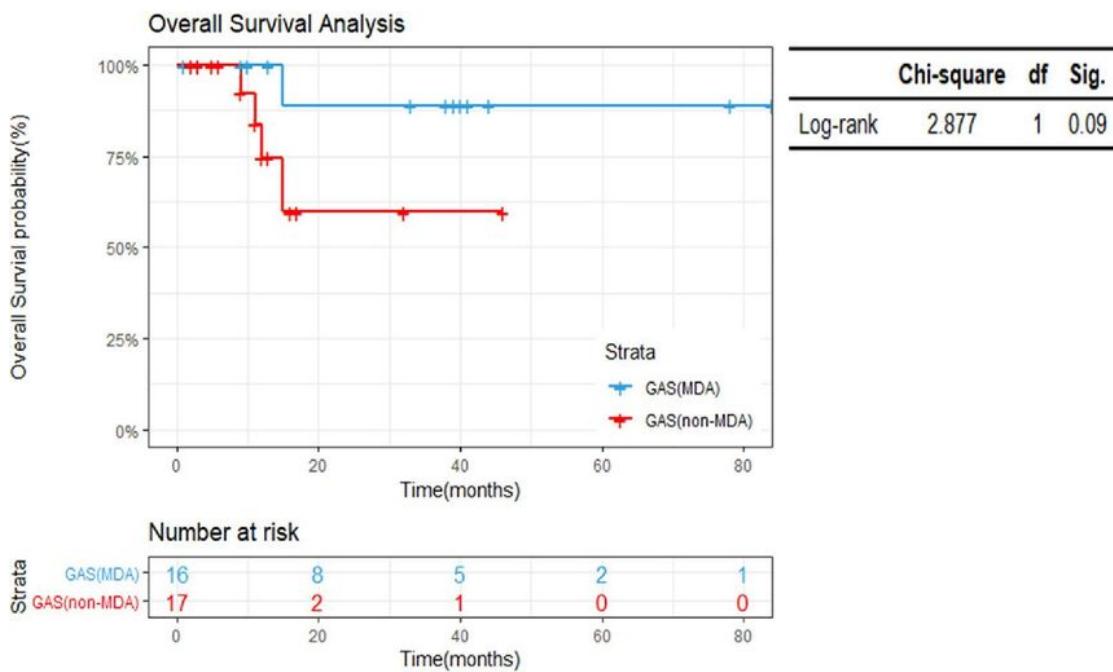
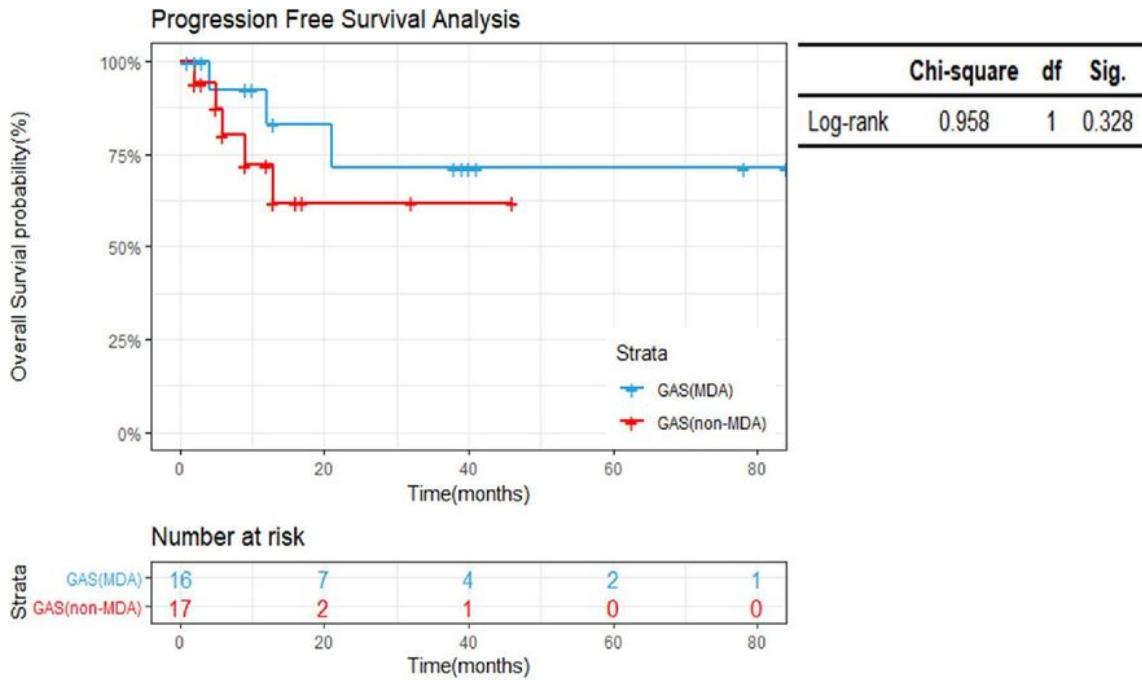


Figure 3

Kaplan-Meier progression free survival and overall survival estimates for MDA vs. non-MDA.
Abbreviations: MDA=minimal deviation ECA.

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