A Retrospective Study on Incidence, Diagnosis, and Clinical Outcome of Gastric-type Endocervical Adenocarcinoma in a Single Institution

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Abstract

Background: Gastric-type endocervical adenocarcinoma is rare but the most common subtype of cervical adenocarcinoma not associated with human papillomavirus. It is more aggressive with a shorter five-year survival rate compared to human papillomavirus-associated usual type endocervical adenocarcinoma. The objectives of our study were to determine the incidence and clinical-pathological characteristics of Gastric-type endocervical adenocarcinoma in a single institution.

Methods: Twenty four cases of invasive cervical adenocarcinoma were identified between January 2000 and December 2015, from the Saskatoon Health Region pathology database using International Endocervical Adenocarcinoma Criteria and Classification to retrospectively classify endocervical adenocarcinoma. Immunohistochemistry was performed with antibodies for Gastric mucin-6 (MUC-6), $p16^{INK4a}$, cyclin-dependent kinase inhibitor 2A (p16), p53 protein (p53), estrogen and progesterone receptors. Clinical and pathological data was retrieved from pathology reports and charts. Statistical analysis was performed using Mann-Whitney U test and Chi-Square test.

Results: Using the International Endocervical Adenocarcinoma Criteria and Classification criteria, 19 cases (79.2%) were classified as human papillomavirus-associated usual type endocervical adenocarcinoma, and five cases (20.8%) as Gastric-type endocervical adenocarcinoma. In our study 40% of Gastric-type endocervical adenocarcinoma cases presented at stage III compared to none of the usual type endocervical carcinoma cases. All the Gastric-type endocervical adenocarcinoma cases were positive for MUC-6, and negative for p16. 60% Gastric-type endocervical adenocarcinoma cases demonstrated mutant type p53 staining. In contrast, 84.2% of human papillomavirus-associated usual type endocervical adenocarcinoma cases showed block like nuclear and cytoplasmic positivity with p16 antibodies. The Gastric-type endocervical adenocarcinoma group had significantly shorter median survival time than human papillomavirus-associated usual type endocervical adenocarcinoma group, Gastric-type endocervical adenocarcinoma is 22 months compared to human papillomavirus-associated usual type endocervical adenocarcinoma at 118 months ($p = 0.043$).

Conclusions: In this study, Gastric-type endocervical adenocarcinoma accounted for 20.8% of all cervical adenocarcinoma with higher stage at presentation and shorter overall survival. Histomorphology and immunohistochemistry for MUC-6 and p16 could differentiate between Gastric-type endocervical adenocarcinoma and human papillomavirus-associated usual type endocervical adenocarcinoma.

Introduction

Uterine cervical carcinoma is the fourth most common malignancy in women worldwide.[1] Adenocarcinoma represents 20-25% of cervical cancers with increasing incidence in recent years. Approximately 80-90% of cervical adenocarcinomas (ECA) are HPV-associated (HPVA), and approximately 10-20% are unrelated to HPV infection (Figure 1).[2-4] Gastric-type endocervical adenocarcinoma (GAS) is the most common subtype of cervical non-HPV-associated adenocarcinoma

(NHPVA) first described in 2007 by Japanese pathologists.[5] GAS is a very aggressive neoplasm with a five-year disease-specific survival rate of 30% compared with 77% in HPV- associated (HPVA) adenocarcinomas of the cervix.[5] These tumors often present at an advanced stage with a tendency for pelvic dissemination, specifically to the ovary, peritoneum, omentum, and distant metastases.[6-9] It displays a histomorphological spectrum from well- to poorly differentiated adenocarcinomas [10-12] and overlaps with HPV-associated (usual, mucinous, invasive stratified mucin producing carcinoma) adenocarcinoma of the cervix. Therefore, a precise diagnosis of this cervical adenocarcinoma variant is the key to adequate management. The objectives of this study were to determine the incidence of GAS in a single institution over the last 15 years and the clinical-pathological features of GAS compared to UEA with clinical outcomes.

Materials And Methods

This retrospective study was approved by the biomedical ethics review board of the University of Saskatchewan. Pathology reports with a diagnosis of adenocarcinoma of the cervix were obtained from the Saskatoon Health Region (SHR) pathology database from January 2000 through December 2015. We identified 159 cases with the search terminology "cervix adenocarcinoma" in the SHR database. Of these, 124 cases were adenocarcinoma *in situ* and 35 cases of invasive adenocarcinoma of the cervix. Slides and reports were available on all of these cases.

The slides were reviewed by two pathologists by simple and reproducible criteria suggested by International Endocervical Adenocarcinoma Criteria and Classification (IECC) into two groups, HPV-associated (HPVA) and non -HPV- associated (NHPVA) by morphologic criteria: easily identifiable apical mitotic figures and apoptotic bodies at scanning magnification as HPVA.[4, 13] The HPV- associated lesions were further subclassified based on cytoplasmic features into usual type (UEA), intestinal type, and signet-ring cell type. Criteria for Gastric-type adenocarcinoma (GAS) included: tumor cells with abundant clear, foamy, or pale eosinophilic cytoplasm and distinct cytoplasmic borders. Minimal deviation adenocarcinoma (MDA)was included as part of a spectrum of GAS. The histopathologic assessment included tumor size, grade, depth of invasion, lymph-vascular space invasion (LVSI), and stage. Representative blocks were selected for immunohistochemical staining. Clinical data were obtained by retrospective review of medical records.

Tissue microarray (TMA) was constructed from paraffin blocks with 6 mm cores in duplicate from two areas of the representative tumor. Immunohistochemistry (IHC) was performed using antibodies for MUC-6, estrogen receptor (ER), progesterone receptor (PR), p16, p53, CK7, CK20, and CEA in dilutions as optimized and validated for routine clinical use.

After initial reassessment of 35 invasive adenocarcinomas, 11cases were reclassified and excluded from our study for the following reasons: endometrial endometrioid adenocarcinoma (5), serous endometrial carcinoma (5), poorly differentiated carcinoma (1). Twenty-four cases were confirmed as invasive adenocarcinoma of the cervix and were reclassified as 19 HPVA- UEA (79.2%) and 5 GAS (20.8%).

Group characteristics were summarized using mean ± standard deviation and counts (percent). Groups were compared using the Mann-Whitney U test and Chi-Square test. When appropriate, the Fisher Exact method was used. Survival time was summarized in months using median and 95% confidence intervals. The Kaplan-Meier estimator and Log Rank test were used to compare survival time between groups. Patients were censored at the last known observation.

Results

The clinical and pathological features of GAS and HPVA-UEA cases are compared in Table 1. The average age at the diagnosis for GAS was 61.6 years (range 43 to 87 years). The presenting clinical symptoms included: watery or bloody vaginal discharge, pelvic pain, heavy post-coital bleeding, irregular vaginal bleeding, and postmenopausal bleeding. The average age at the time of diagnosis for UEA was 44.6 years (range 26 to 62 years). The clinical presentation in this group of patients was very similar to the GAS cases, including asymptomatic patients.

Histology:

All the cases of HPVA-UEA demonstrated apical mitotic figures and apoptotic bodies at scanning magnification. Seventeen showed decreased cytoplasmic mucin (HPVA-UEA), one with intracytoplasmic mucin (mucinous), and one with signet ring cell type cells.

Five cases did not demonstrate the above features. Two of these cases were diagnosed as MDA on initial cervical biopsy and resection specimen. Both of these cases showed classic morphologic features of MDA as extremely well-differentiated, deeply infiltrating, deceptively bland endocervical glands, some with complex outlines. There were also foci of associated lobular endocervical glandular hyperplasia (LEGH). On the other hand, all three cervical biopsies of GAS were diagnosed as HPV-UEA (2) and one as serous carcinoma suggesting difficulties in diagnosis and lack of awareness of GAS diagnostic criteria. However, using IECC criteria, these cases were correctly diagnosed as GAS on review for this study. All three cases of GAS demonstrated well-differentiated (MDA-like) to moderately differentiated areas with variable-sized, deeply infiltrating, and focally crowded neoplastic glands. The columnar epithelium showed voluminous pale eosinophilic cytoplasm, distinct cell borders with moderately enlarged slightly hyperchromatic round nuclei with irregular membranes. Rare mitotic figures and basal apoptotic bodies were noted on high magnification.

Immunohistochemistry:

All the five cases of GAS were diffusely positive for CK7, MUC-6, three cases were strongly and diffusely positive for p53 (mutant type), and two showed a wild-type expression pattern (normal pattern). Four of the cases stained negative for ER, PR and one showed focal, weak ER/PR positivity. Three cases were positive for CEA, and one case was positive for CDX2, supporting intestinal differentiation. Sixteen (out of 19) cases of UEA (84.2%) demonstrated diffuse, block-like nuclear and cytoplasmic positivity for p16

and seventeen cases were negative for CDX-2, MUC-6, and CK20. p53 demonstrated wild-type staining in 15 UEA cases. Three cases were focally positive for ER and one for PR (Table 1).

Treatment and follow up:

Local recurrence/metastasis occurred in 10 (3/5 GAS, 7/19 HPVA-UEA) of the 24 patients (Table 2).

Five of nineteen HPVA-UEA patients with recurrence were stage IIB, one stage IIA and one Stage IB, with two found to have a distant recurrence, two both local and distant recurrences, and three local recurrences with pelvic lymph node involvement died of renal complications. Two of the recurrent cases had mucinous, NOS, and signet ring cell type adenocarcinoma, respectively. All the patients with local and distant recurrences received palliative treatment with either one or more lines of systemic chemotherapy or local palliative radiation and or both in accordance with national guidelines after being discussed in Multidisciplinary Gynecologic Oncology tumor rounds.

Death was observed in three GAS patients and six of the HPVA-UEA patients. Time to death varied from 18-108 months, respectively. As shown in Figure 3, the GAS group had a significantly shorter median survival time than the UEA group (GAS=22.0 months (95%CI 15.6, 28.4) vs. UEA=118.0 months (95%CI 59.4, 176.6), p=0.043).

Discussion

Adenocarcinomas of the cervix (ECA) account for approximately 20-25 % of cervical carcinomas, of which 80-90% are related to HPV infection, and the remaining are NHPVA. HPVA-UEA patients are younger, usually present at an early stage, and have a better prognosis compared to NHPVA. Non-HPV-associated GAS patients are usually older, present at a late stage, have poor outcomes, and should be correctly recognized in cervical biopsy specimens for better patient management. ECAs are classified according to the WHO system predominantly based on cytomorphological features into more than ten different types and are confusing for both pathologists and clinicians[4]. Recently, IECC has validated the ECA classification system based on simple morphologic criteria into two etiologic groups: HPVA-UEA and NHPVA, using easily identifiable apical mitotic figures and apoptotic bodies at scanning magnification.[13-16] We found these criteria to be simple and reproducible. In our study, GAS was also the most common subtype of NHPVA, accounting for 20.8% of all ECA. The exact incidence of GAS in North America is not yet known, but larger multi-institutional international studies reported it as 10% and up to 20- 25% in the Japanese population.[5,13,17]

Malignant gastric-type cervical lesions comprise MDA and GAS. The patients usually present with watery discharge or enlarged cervix (barrel cervix -due to axially and radially infiltrating neoplastic glands). These lesions usually arise in the upper endocervix in contrast to HPVA-UEA, which arise in the transformation zone and present as a mass lesion. MDA is a well-differentiated morphologic spectrum of GAS. MDA usually shows very deceptively bland, deeply infiltrating glands in the wall of the cervix. Therefore, it is very challenging to establish a malignant diagnosis of MDA in superficial biopsies; thus, a high index of

suspicion and radiological correlation is required. In our two MDA cases, the clinical history, enlarged cervix, and corresponding radiological findings, along with deep cervical biopsies, aided in guiding the histologic diagnosis. The histologic features/grading in MDA is important in reaching a correct diagnosis but has no impact on clinical outcomes. One of our cases presented at an early stage, while the second case had locally advanced disease at the time of diagnosis. Therefore the umbrella term GAS is recommended for these lesions.[4-13]

The histologic features of GAS are still under-recognized. Three of our five cases were diagnosed as HPVA-UEA or serous carcinoma on biopsy specimen due to under-recognition of histologic features of GAS and/or lack of routine use of p16 or misinterpretation of p53 staining for serous carcinoma. The key cytoplasmic features of GAS are similar to MDA.[4,5,13] However, nuclei may vary from uniform, round bland, basally located as noted in MDA to moderate, marked atypia with enlargement, and irregular cell membranes in moderately to poorly differentiated GAS. [10,12]

These cytological features of GAS overlap with HPVA-UEA mucinous adenocarcinoma (mucinous NOS, intestinal and signet ring carcinoma), endometrial endometrioid, and serous endometrial carcinoma.[13-16] IECC criteria are simple and reproducible to differentiate between HPVA-UEA and NHPVA-ECA. The diagnosis should be confirmed by immunohistochemistry for p16/HPV, MUC-6, and p53. P16 is a surrogate marker for HPV-related malignant lesions and is a useful adjunct in confirmation of UEA on cervical biopsy. If it is negative or shows a mosaic pattern, MUC-6 and p53 IHC may aid in the diagnosis of GAS. The immunohistochemical profile of GAS is similar to normal gastric mucinous cells with expression of MUC-6, HIK 1083. In this study, all the GAS cases were MUC-6 positive and p16 negative. 60% of cases demonstrated mutant type staining pattern with p53 antibody. MUC-6 was positive in 40-100 % in larger studies, and mutant type p53 staining pattern was noted in 40-52% of cases. [5, 14, 18-21]

GAS usually arises in the upper endocervix and may extend to the lower uterine segment. On cervical biopsy specimens, differential diagnosis of GAS also includes mucinous endometrial endometrioid adenocarcinoma. These are FIGO grade I adenocarcinomas, ER, PR positive with an excellent prognosis. ER, PR immunohistochemistry can differentiate between these two entities on the biopsy specimen. Approximately 50% of GAS cases are positive for p53 and must be differentiated from serous endometrial carcinoma, which is positive for p16, ER, and PR. The surgical management of these two entities is different from endocervical carcinoma.

Our study showed a higher rate of recurrence and metastasis in GAS compared to other studies that reported recurrence in 31 to 45% of cases. This may be due to the small sample size of our study. The median survival among those with GAS was 22 months compared to 118 months among those with UEA. This is consistent with larger studies.[5,6,7, 21].The poorer outcome may be related to GAS being more resistant to both radiotherapy and chemotherapy. Our results also demonstrate that recurrent HPVA-UEA cases had a better response to adjuvant chemotherapy and radiotherapy compared to patients with GAS.

In conclusion, this study emphasizes the importance of awareness of GAS, its diagnostic dilemmas and the need to recognize clinical, morphological features of GAS, the significance of IECC criteria to differentiate between HPVA and non-HPV associated ECA, and the role of p16, MUC-6, and p53 immunohistochemistry in differential histopathological diagnosis. GAS usually presents at an advanced stage and therefore, ovarian conservation may not be recommended, and omentectomy should be considered as part of surgical management. The cause of aggressive natural history remains unknown, maybe due to lack of early detection on PAP smears, diagnostic challenges, and resistance to therapy. ECA are heterogeneous tumors with different etiologies and driver mutations but are being treated with a universal approach. There is a need for further studies to characterize additional chemotherapeutic agents or optimal radiotherapy than similar protocols used for recurrent UEA.

Declarations

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Availability of data and materials:

All data generated or analyzed during this study are included in this manuscript.

Ethics approval and conset to participate:

Approved by instituitional Biomedical Ethics Committee.

Consent for Publication:

Institutional consent.

Competing Interests:

None.

Authors Contributions:

AR, RC: designed the study, performed histologic examination, analysed data and wrote the manuscript.

DL: Reviewed the charts, extracted clinical information and did statistical analysis.

AA: Reviewed charts, extracted and interpreted clinical information, manuscript writing.

HN: constructed tissue microarray for immunohistochemistry.

NK, ET: Optimized and performed immunohistiochemistry.

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Tables

Table 1. Comparisons and differences between GAS and UEA regarding stage, age, lymph-vascular permeation, lymph node status and local/distant metastases at the time of diagnosis. All data presented as count (percent), unless otherwise specified.

	GAS N=5	UEA N=19	P-Value
FIGO			
I	2 (40)	11 (57.9)	0.31[a]
II	1 (20)	8 (42.1)	
III	2 (40)	-	
IV	-	-	
Age (years), mean ± SD	61.6 ± 16.5	44.3 ± 9.0	0.015[a]
Tumor Size (cm), mean ± SD	3.8 ± 0.8	1.9 ± 1.2	0.004[a]
LVI			
Present	3 (60)	3 (15.8)	0.079[b]
Not Present	2 (40)	12 (63.2)	
Unknown	-	4(21.1)	
Regional Lymph Node Mets			
Present	1 (20)	2 (10.5)	0.52[b]
Not Present	4 (80)	14 (73.7)	
Unknown	-	3 (15.8)	
Abdominal Spread	3 (60)	-	0.0049
Other Mets	2 (40)	-	0.0362
Recurrence			
Yes	3 (60)	7 (36.8)	0.63[b]
No	2 (40)	10 (52.3)	
Unknown	-	2 (10.5)	
P16			
Positive	-	16 (84.2)	0.043[c]
Negative	5 (100)	0 (0)	
Unknown	-	3 (15.8)	
MUC-6			
Positive	5(100)	-	<0.0001[c]

Negative	-	17 (89.5)	
Unknown	-	2 (10.5)	
P53			
Positive	3 (60)	-	0.0049[c]
Negative	2 (40)	17 (89.4)	
Unknown	-	2 (11.6)	

a – Mann Whitney U test,
b – Fisher Exact comparing Present vs Not Present or Unknown,
c – Fisher Exact comparing Positive vs Negative or Unknown

Table 2. Characteristics of treatment and follow up. All data presented as count (percent), unless otherwise specified.

	GAS N=5	UEA N=19	P-Value
Treatment			
Radical Hysterectomy	4 (80.0)	12 (63.2)	0.63
Chemotherapy	2 (40.0)	3 (15.8)	0.27
Radiation Therapy	3 (60.0)	5 (26.3)	0.29
Pelvic Exenteration	1 (20.0)	0 (0.0)	0.21
LEEP	0 (0.0)	9 (47.4)	0.19
Cervical Biopsy	0 (0.0)	2 (10.5)	0.99
Recurrence			
Yes	3 (60.0)	7 (36.8)	0.61
Not Observed	2 (40.0)	12 (63.2)	
Death			
Yes	3 (60.0)	6 (31.6)	0.33
Not Observed	2 (40.0)	13 (68.4)	
Time to Death (months)			
Median (95% CI)	22.0 (15.6, 28.4)	118.0 (59.4, 176.6)	0.043[a]

a – Test of equality of survival distributions using the Kaplan-Meier Estimator and Log Rank test.

Figures

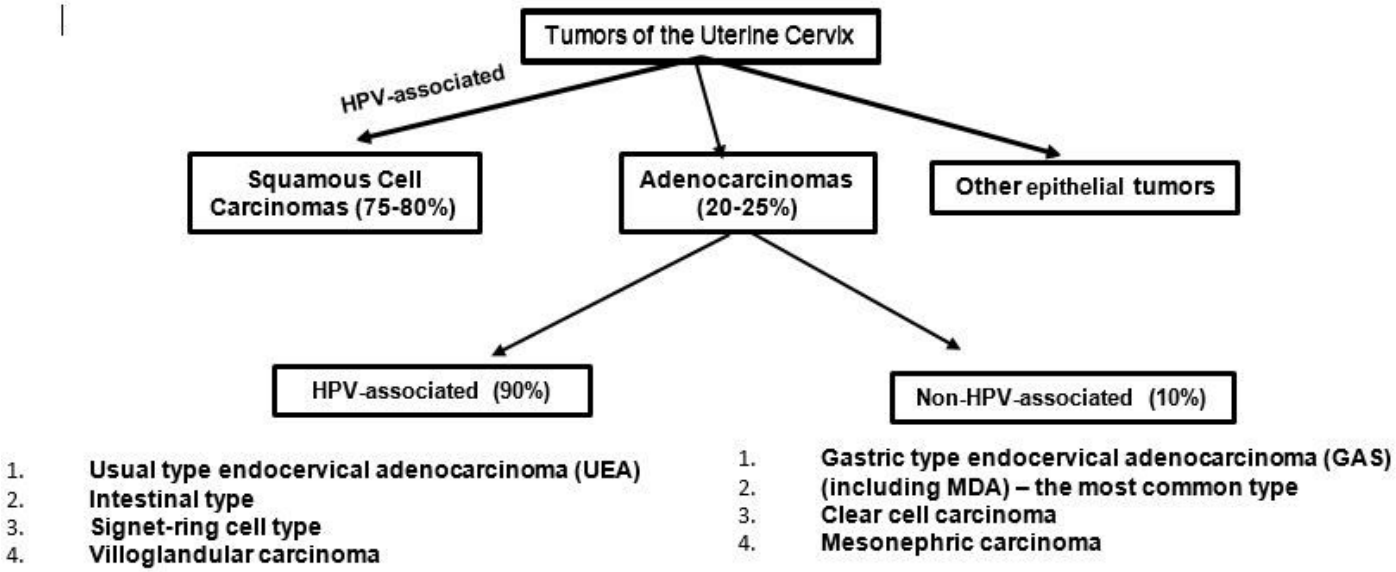

Figure 1

Classification and association of tumors of the uterine cervix

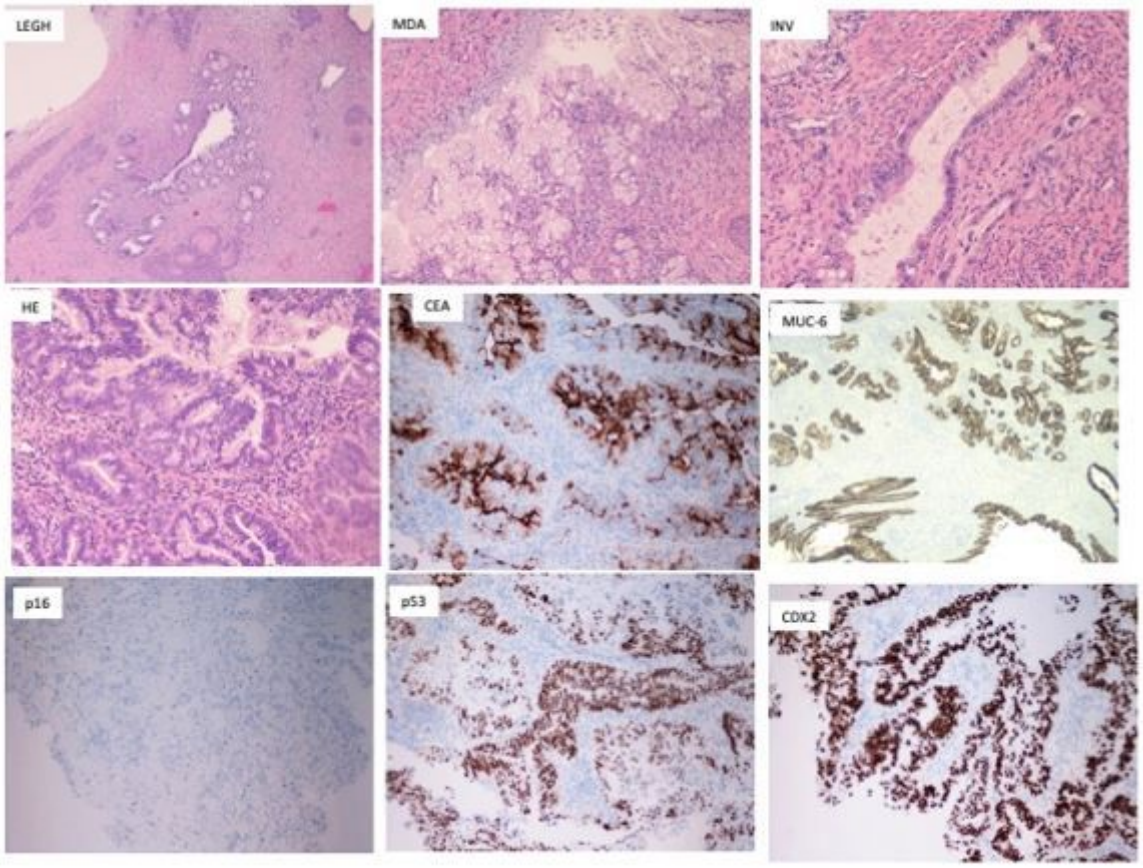

Figure 2

Images from well-differentiated MDA (B), arising on the base of LEGH (A) with centrally dilated duct surrounded by small proliferating glands. B. MDA with intraluminal papillary infoldings lined by columnar pale cells with abundant mucin, distinct cell borders and very mild nuclear enlargement. C. Focus on stromal invasion by single and small clusters of neoplastic cells. D. HE of moderately-differentiated GAS with columnar pale to eosinophilic cells with nuclear enlargement, stratification and hyperchromasia. Dispersed goblet cells are present Single images of IHC with different antibodies E. CEA, F. MUC-6 G.p16 H.p53 and I.CDX2

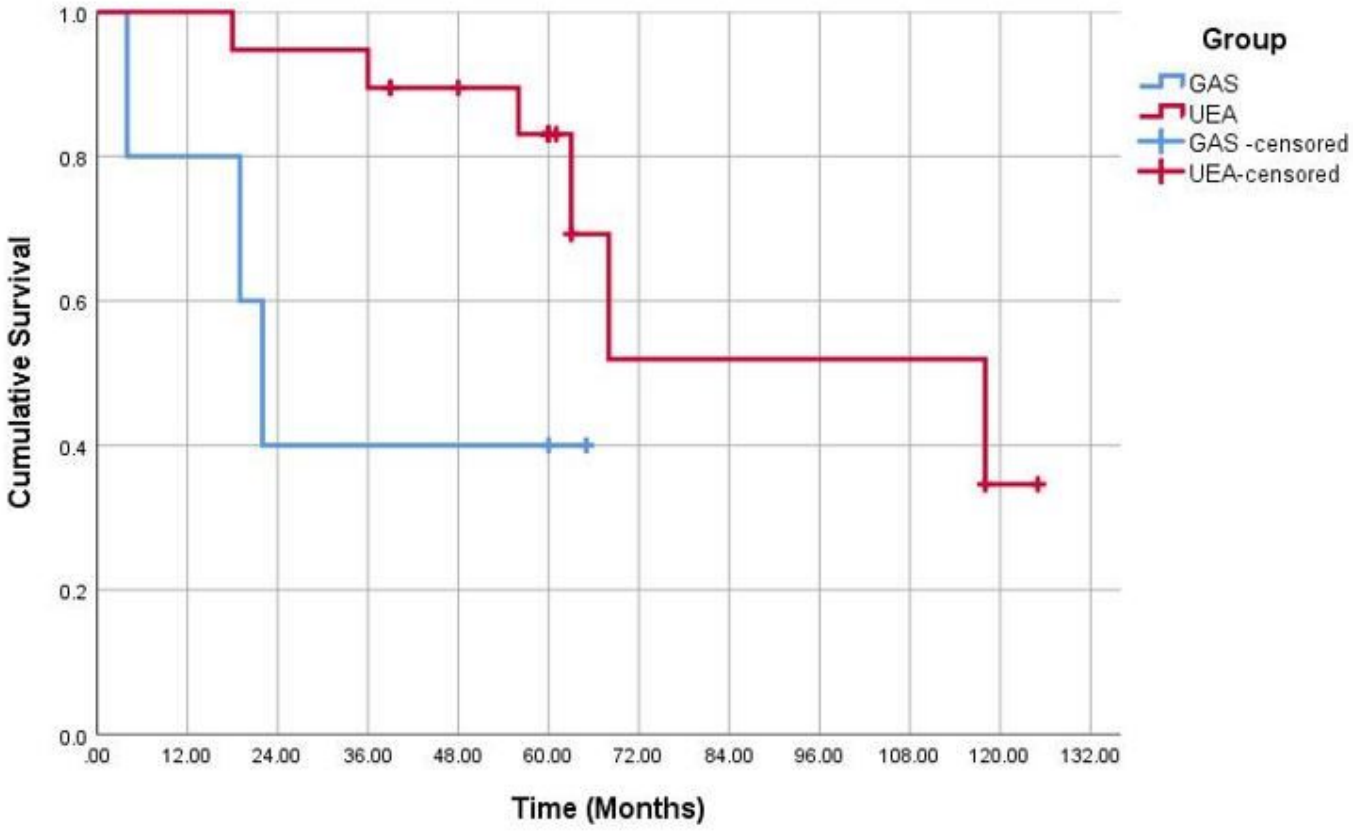

Figure 3

Kaplan-Meier Curve of the time to death in months among the GAS and UEA patients. Test of equality of the survival distributions was assessed using the Log Rank test (p=0.043).