Published in final edited form as:

Am J Surg Pathol. 2015 November ; 39(11): 1449–1457. doi:10.1097/PAS.0000000000000532.

Gastric type endocervical adenocarcinoma: an aggressive tumor with unusual metastatic patterns and poor prognosis

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Abstract

Gastric type adenocarcinoma of the uterine cervix (GAS) is a rare variant of mucinous endocervical adenocarcinoma not etiologically associated with human papillomavirus (HPV) infection, with minimal deviation adenocarcinoma (MDA) at the well-differentiated end of the morphologic spectrum. These tumors are reported to have worse prognosis than usual HPV-associated endocervical adenocarcinoma (UEA). A retrospective review of GAS was performed from the pathology databases of three institutions spanning 20 years. Stage, metastatic patterns, and overall survival were documented. Forty GAS cases were identified, with clinical follow-up data available for 38. The tumors were subclassified as MDA (n=13) and non-MDA GAS (n=27). Two patients were syndromic (one Li-Fraumeni, one Peutz-Jeghers). At presentation, 59% were advanced stage (FIGO II–IV), 50% had lymph node metastases, 35% had ovarian involvement, 20% had abdominal disease, 39% had at least one site of metastasis at the time of initial surgery, and 12% of patients experienced distant recurrence. The metastatic sites included lymph nodes, adnexa, omentum, bowel, peritoneum, diaphragm, abdominal wall, bladder, vagina, appendix, and brain. Follow-up ranged from 1.4 to 136.0 months (mean, 33.9 months); 20/38 (52.6%) had no evidence of disease, 3/38 (7.9%) were alive with disease, and 15/38 (39.5%) died of disease. Disease specific survival at 5 years was 42% for GAS vs. 91% for UEA. There were no survival differences between MDA and non-MDA GAS. GAS represents a distinct, biologically aggressive type of endocervical adenocarcinoma. The majority of patients present at advanced stage and pelvic, abdominal, and distant metastases are not uncommon.

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Conflicts of Interest: The authors have no conflicts to declare.

Keywords

cervix; carcinoma; adenocarcinoma; HPV; gastric; lobular endocervical glandular hyperplasia; minimal deviation; clinical outcomes; metastasis

Introduction

Endocervical adenocarcinoma (ECA) represents approximately 20–25% of cervical cancers, with increasing incidence in recent years.^{1–5} The 2014 World Health Organization (WHO) Classification of Tumours of Female Reproductive Organs includes gastric type adenocarcinomas as a variant of mucinous endocervical adenocarcinomas (Table 1).⁶ By far the most common type of adenocarcinoma is the usual type (UEA); this is associated with high-risk human papillomavirus (HPV) infection, most commonly HPV types 16 and 18. However, unlike cervical squamous cell carcinoma (SCC) where nearly all cases are etiologically associated with HPV infection, approximately 10% of ECAs in Western countries are unrelated to HPV.^{7,8} Therefore, ECA can be subclassified into HPV-associated and HPV-unassociated groups (Table 2). The HPV-associated ECAs can have a variety of morphological appearances, including mucinous features, with or without intestinal differentiation, and they may resemble endometrioid and serous carcinomas. The HPV-unassociated group includes clear cell, mesonephric, and gastric type, including minimal deviation adenocarcinomas (MDA), also known as adenoma malignum.^{9–11}

MDA are characterized by deceptively low histologic grade, often with neoplastic glands almost indistinguishable from benign endocervical glands.^{12–16} They exhibit abundant apical mucin, basally oriented nuclei, and, characteristically, little or only very subtle cervical stromal reaction to invasion, making it difficult to diagnose in cervico-vaginal cytology preparations, biopsies, conization specimens, and even hysterectomies. Sometimes deep cervical stromal involvement may be the only overt feature supporting a malignant diagnosis. Clinical outcomes in MDA have been a matter of considerable debate with several studies indicating its aggressive biologic nature, especially compared to UEA,^{12,14,16} whereas other reports have stated that the difference may not be independent of stage.¹⁷ Additionally, MDA has been linked to Peutz-Jeghers syndrome in up to 10% of cases.^{18–20}

Several recent studies have described a new category of mucinous endocervical adenocarcinoma, gastric type adenocarcinoma (GAS), which has a distinctive histological appearance and immunohistochemical (IHC) profile as well as poor clinical outcomes.^{9,16,20} Histologic criteria for GAS were first defined by Kojima et al. to include cells showing clear and/or pale eosinophilic and voluminous cytoplasm with distinct cell borders comprising the majority of the tumor.¹⁶ In some cases benign endocervical glands showing ‘gastric metaplasia’ resembling normal pyloric glands of the antral stomach are found adjacent to invasive adenocarcinoma, and these tumors frequently contain areas that are indistinguishable from MDA. There is histochemical, immunohistochemical, and etiologic overlap as well: both lesions feature acidic mucin and an immunohistochemical profile similar to normal gastric mucus cells, with expression of HIK1083, lysozyme, and

pepsinogen II.^{13,16} They are negative for HPV DNA (by PCR) and p16 (by immunohistochemistry), with only rare exceptions.

The term ‘lobular endocervical glandular hyperplasia’ (LEGH) was first coined by Nucci et al. to describe a benign pseudoneoplastic endocervical process resembling MDA.²¹ Almost simultaneously, Mikami et al. described a series of similar lesions using the terminology “pyloric gland metaplasia.”²² Subsequently, LEGH was shown to have features of gastric metaplasia and, similar to GAS, had a gastric-type IHC profile,^{23–27} prompting some authors to consider LEGH to be a putative precursor lesion to MDA and GAS.^{23,26,28,29}

Kojima’s landmark study looked at only 16 cases of GAS (including MDA).¹⁶ Here, we characterize the clinical outcomes of patients with GAS (including MDA), focusing not only on overall survival, but also on other clinical variables such as sites of metastasis and recurrence.

Materials and Methods

Patients diagnosed with GAS at Memorial Sloan Kettering Cancer Center (MSK) from January 1, 1997 to January 1, 2012 were identified. Additional cases (spanning the period between January 1, 1998 and January 1, 2009) were also included from two collaborating institutions (Jikei University, Tokyo, Japan; Yale University School of Medicine, New Haven, CT, USA).

Hematoxylin and eosin stained histologic sections were reviewed by two pathologists (YSK and KJP) and the diagnoses were established using criteria described by Kojima et al.¹⁶ Specifically, tumors showed voluminous clear and/or pale eosinophilic cytoplasm with distinct cell borders in a significant portion of the tumor. None of the tumors showed the typical features of usual type endocervical adenocarcinoma (columnar nuclei with abundant apoptotic bodies and luminal mitotic figures). The results of p16 immunohistochemistry performed for diagnostic purposes in any case were also recorded. All relevant pathologic and clinical data were collected and analyzed. Recurrent histologic findings, including association with LEGH, were recorded and analyzed. The findings were compared to a cohort of 158 usual HPV-associated endocervical adenocarcinomas identified at MSK between January 1, 2002 and January 1, 2012.

While we consider MDA to be a part of the morphologic spectrum of GAS, we collected separate data for these tumors for the purposes of this study to determine whether there were associations between histologic differentiation and clinical biology. Tumors were classified as MDA when the bulk of tumor in the cervix (≥ 90%) was cytologically low grade (minimal nuclear atypia, abundant apical mucin) with well formed glands sometimes showing the classically described “claw-like” growth pattern and some stromal desmoplasia. Any cases where the presence of an invasive tumor was equivocal by histologic standards were excluded from our study. Tumors were classified as non-MDA when at least 10% of the tumor in the cervix revealed high grade nuclei, prominent nucleoli, significant architectural complexity (more complex than simple glandular, cystic, or claw-shaped), single cells or clusters, or obvious extensive destructive stromal invasion.

Statistical significance of the differences in proportions of cases within each histologic group having various pathologic or clinical features were made using Fisher's exact test.³⁰ The survival time of each patient was calculated from the date of diagnosis to date of death with right-censoring at date of last follow-up for the patients who were still alive. The cumulative survival probabilities for each group of patients were estimated by life table methods, commonly referred to as the method of Kaplan and Meier.³¹ The log-rank test was used to compare two survival curves.^{32,33} The standard errors associated with the survival probabilities at a given time point were calculated from the life table by a modification of the method of Greenwood.^{34,35}

Results

Forty cases were identified (MSK – 29 cases, Chiba University – 9 cases, and Yale University – 2 cases) for which treatment information was available. Follow-up information was collected for 38 cases, as 2 patients were lost to follow-up. Stage at presentation was recorded in all but one patient. All cases were diagnosed and evaluated based on sampling of the cervix (biopsy, curettage, Loop Electrocautery Excision Procedure [LEEP], hysterectomy, trachelectomy, exenteration) except for one case where the only material available was from a peritoneal biopsy. GAS cases were further subclassified as MDA (n=13) or non-MDA (n=27).

Histologically, the tumors showed the features described by Kojima et al. (Fig. 1A). Additional notable features included presence of LEGH in 20% of the tumors (50% of MDA and 3.8% of non-MDA GAS) (Fig. 1B); cellular dyshesion, single cell infiltration, and signet ring differentiation, especially in the non-MDA tumors and particularly prominent at the advancing edge of the cervical stromal invasion; and focal intestinal differentiation in the form of goblet (26%) or Paneth-like neuroendocrine cells (11%) (Fig. 1C). Lobular endocervical glandular hyperplasia was usually superficially located in the cervix, often admixed with adjacent invasive carcinoma but not always.

The mean age at time of GAS diagnosis was 49.8 years (range, 30.3 to 66.8 years), and the mean follow-up period was 33.9 months (range, 1.4 to 136.0 months). Twenty out of 38 (52.6%) patients showed no evidence of disease (NED), 3/38 (7.9%) were alive with disease (AWD), and 15/38 (39.5%) had died of disease. Separating non-MDA from MDA gastric-type adenocarcinomas revealed similar results between the two groups: mean age 49 vs 49.8; NED 13/26 (50%) vs 6/12 (50%); AWD 3/26 (12%) vs 0/12 (0%); and DOD 10/26 (38%) vs 6/12 (50%) respectively (Table 3).

In comparison, treatment and clinical follow-up information was available in 139 UEA cases. The mean age at time of diagnosis for UEA was 40.5 years (range, 18.2 to 82.5). The mean follow-up period was 50.6 months (range, 1.2 to 196.1 months). One hundred twenty-six out of 139 (91%) patients were NED, 1/139 (1%) AWD, and 12/139 (8%) DOD (Table 3). Prior medical histories are summarized in Table 4. One patient had a history of Peutz-Jeghers syndrome and another had a history of Li-Fraumeni syndrome. Two patients had histories of breast cancer, 1 patient had history of colon cancer, 1 had Wilms tumor, pheochromocytoma, and renal cell carcinoma, and 1 patient developed a subsequent

mucinous bronchioloalveolar carcinoma of the lung. The Li-Fraumeni patient also had a history of breast carcinoma. The other 33 patients had no significant past medical histories. Information regarding stage distribution at the time of initial surgery/biopsy is summarized in Table 5 and Figure 2. The majority of patients with GAS/MDA presented at advanced stage (59% stage II–IV), with only 41% presenting at stage I. Comparing non-MDA vs MDA tumors showed no statistical difference in stage at presentation (31 vs 62% stage I, 69 vs 38% stage II–IV, respectively, $p=0.091$). In comparison, the UEA patients mostly presented at stage I (89%), with only 11% presenting at high stage (stage information available in 139 UEA patients). This difference was statistically significant from GAS/MDA ($p<0.0001$). Additional routinely assessed pathologic variables included lymphovascular invasion, regional and remote lymph node involvement, ovarian and fallopian tube metastases, spread to pelvic and abdominal sites, and distant extraperitoneal spread. Notably, nearly 35% had ovarian involvement, 20% had abdominal disease, and 12% experienced extraperitoneal recurrences (see Table 6 for details). GAS tumors had higher incidences of these high risk features as compared to UEA and there was no difference between MDA and non-MDA tumors.

GAS had significantly worse disease specific survival (DSS) than UEA (Figs. 3A and 3B). Five- and 10-year survival data were calculated for all stages and for stage I only for both GAS and UEA (Table 7A). As expected, the 5-year DSS for stage I UEA was excellent at 96%, compared to 62% for stage I GAS. When MDA cases were extracted from the group of gastric type adenocarcinomas, there was no statistically significant difference in survival or recurrence rates based on histologic differentiation (Table 7B and Fig. 4).

As mentioned previously, two patients had known familial syndromes. One patient had Peutz-Jeghers syndrome with the diagnosis of endocervical adenocarcinoma (MDA including LEGH) being the sentinel event at age 39. She presented with stage IV disease (pT3b pN0 pM1) with peritoneal and omental involvement and underwent initial surgical management with supracervical hysterectomy, bilateral salpingo-oophorectomy, lymph node dissection, and peritoneal debulking, followed by chemotherapy and radiation and subsequent completion radical trachelectomy. She currently has no evidence of disease and no evidence of any other syndrome-associated neoplasia.

The second patient was diagnosed with Li-Fraumeni syndrome at the age of 30. She had a history of bilateral breast cancer at the age of 22, for which she was treated with bilateral mastectomy, chemotherapy, and tamoxifen. She presented with stage IIA2 GAS (pT2a2 Nx Mx) at age 30. She was initially managed with radiation and chemotherapy but within 6 months developed another malignancy, a diffuse astrocytoma (WHO grade II) that was managed with local radiation. The patient developed metastatic GAS to retroperitoneal lymph nodes 2 years later, and metastatic GAS to bone and cerebellum 2 years after that (Fig. 5).

Twelve GAS patients developed recurrences compared to 6 UEA patients; this was statistically significant. The number of cases was small so there was no difference between GAS and UEA regarding sites of recurrence. Table 8 lists the sites of recurrence for each patient and whether they had MDA or non-MDA GAS histologic type.

Discussion

Mucinous adenocarcinomas of the endocervix demonstrate significant clinical, etiologic, and morphological diversity and many are unassociated with HPV infection.^{7,8} The 2014 World Health Organization classification of mucinous endocervical adenocarcinomas lists the following subtypes: gastric, intestinal, and signet ring-cell type, with minimal deviation/adenoma malignum a synonym for gastric type adenocarcinoma when extremely well differentiated.⁶ Our work and that of other investigators support the conclusion that gastric type endocervical adenocarcinoma/minimal deviation adenocarcinoma constitutes a unique tumor type with distinct etiologic, morphologic, immunohistochemical, and clinical features that set it apart from other mucinous endocervical adenocarcinomas^{9,16,36,37} (Table 9). This work confirms conclusions offered by Kojima and colleagues and builds on them. Gastric type adenocarcinoma of the endocervix is a clinically aggressive neoplasm with a distinctive histologic appearance. Mucinous minimal deviation adenocarcinoma (adenoma malignum) is a morphologically well-differentiated variant of this tumor type. Despite a high degree of histologic differentiation, it is as clinically aggressive as less differentiated varieties. There was no significant difference in age, stage, disease distribution or outcomes between those tumors classically defined as minimal deviation adenocarcinoma vs. less well-differentiated gastric-type adenocarcinomas.

While we show that gastric type adenocarcinomas typically present at a higher stage than HPV-associated adenocarcinomas of the usual endocervical type, survival analysis restricted to FIGO stage I tumors indicates that the gastric type adenocarcinomas remain more aggressive. Unlike HPV-associated UEA, which typically remain localized to the pelvis (while sparing ovaries) and regional lymph nodes until late in the disease course, GAS frequently metastasize to ovaries, the abdomen, the omentum (Fig. 6), and distant sites. Rare affected patients have a familial cancer predisposition syndrome.

It is important for pathologists to be able to recognize this type of endocervical adenocarcinoma because of its distinguishing clinical features. With large-scale HPV vaccination programs and the projected decrease in the prevalence of HPV-associated adenocarcinomas, there is potential increase in the proportion of gastric type endocervical adenocarcinomas, making early and accurate recognition even more important. Unlike HPV-associated endocervical adenocarcinomas of usual type, gastric type adenocarcinomas, including minimal deviation type, are frequently centered in the upper endocervix,³⁸ present with a bulky cervix,³⁹ are usually p16-negative or focal, demonstrate gastric differentiation, and may contain lobular endocervical glandular hyperplasia, its putative precursor.^{9,16,23,40–43} We presented a more extensive description of the morphologic spectrum of these tumors in abstract form recently (manuscript in preparation)⁴⁴; we hope this helps pathologists better recognize these distinct tumors.

Similar to the data presented by Kojima's group, we report significantly worse survival outcomes for gastric type adenocarcinoma compared to usual endocervical adenocarcinoma. Gastric type adenocarcinomas of the uterine cervix, including those traditionally classified as minimal deviation adenocarcinoma, are a distinct subset of tumors unassociated with high-risk HPV infection which have a much more aggressive phenotype and display unusual

metastatic patterns compared to usual type endocervical adenocarcinoma. Patients tend to present at higher stage and, even when matched for stage I, have worse disease specific survival. Metastatic sites include omentum, liver, brain, and bone; these are uncommonly involved organs in endocervical adenocarcinoma. It is extremely important for pathologists to be able to recognize this rare tumor because of its aggressive nature and the diagnostic difficulties it can pose. Dependence on p16 reactivity to distinguish cervical adenocarcinoma from a benign process is a major pitfall in this tumor subtype. This also challenges the appropriateness of moving toward HPV-only testing as a screening tool for cervical cancer since these tumors will surely be missed by such testing alone.

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Figure 1.

Figure 1A. Gastric type endocervical adenocarcinoma with voluminous clear cytoplasm and basally located nuclei with moderate cytologic atypia, adjacent small invasive tumor clusters (H&E 100×).

Figure 1B. Lobular endocervical glandular hyperplasia with central dilated gland and smaller glands proliferating along the periphery, similar to pancreatic ducts (H&E 40×)

Figure 1C. Goblet cell and neurosecretory-like granules in glands of gastric type adenocarcinoma (H&E 200×)

Stage I vs. II-IV

Figure 2.

Disease stage distribution at presentation (GAS vs. UEA).

Abbreviations: GAS=gastric type adenocarcinoma of the uterine cervix. UEA=usual endocervical adenocarcinoma.

Figure 3.

Figure 3A. Kaplan-Meier disease-specific survival estimates for UEA vs. GAS, all stages.
 Figure 3B. Kaplan-Meier disease-specific survival estimates for UEA vs. GAS, stage I only.
 Abbreviations: GAS=gastric type adenocarcinoma of the uterine cervix. UEA=usual endocervical adenocarcinoma.

Figure 4. Kaplan-Meier disease-specific survival estimates for MDA vs. non-MDA GAS. Abbreviations: GAS=gastric type adenocarcinoma of the uterine cervix. MDA: minimal deviation adenocarcinoma.

Figure 5. Metastatic gastric type adenocarcinoma to brain; tumor appears well differentiated with small basally located nuclei with little cytologic atypia infiltrating glial tissue (H&E 20×).

Figure 6. Metastatic gastric type adenocarcinoma to omentum; well differentiated glands with eosinophilic and mucinous cytoplasm diffusely infiltrating adipose tissue and eliciting desmoplastic reaction (H&E 40×).

Figure 7.

Figure 7A. Well formed glands of gastric type adenocarcinoma diffusely infiltrating cervical wall (H&E 20×).

Figure 7B. Tumor shows moderate to severe nuclear atypia with voluminous clear cytoplasm and distinct cell membranes; the severe nuclear atypia is incongruous with well differentiated glands (H&E 100×)

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Table 1

WHO 2014 classification of glandular tumours of the uterine cervix.

Glandular tumours and precursors
Endocervical adenocarcinoma, usual type
Mucinous carcinoma, NOS
Gastric type
Intestinal type
Signet-ring cell type
Villoglandular carcinoma
Endometrioid carcinoma
Clear cell carcinoma
Serous carcinoma
Mesonephric carcinoma
Adenocarcinoma admixed with neuroendocrine carcinoma

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Classification of endocervical adenocarcinoma based on association with HPV infection and histologic features.

Table 2

HPV associated
Mucinous adenocarcinoma
Endocervical
Intestinal
Signet-ring
Villoglandular
HPV unassociated
Clear cell carcinoma
Mesonephric carcinoma
Gastric type (GAS)
Minimal deviation adenocarcinoma (MDA)
HPV association controversial
Endometrioid
Serous

Table 3

Summary of clinical outcomes

Outcomes	GAS (n=38) n (%)	UEA (n=139) n (%)	P value*
NED	20 (52.6)	126 (91)	<0.001
AWD	3 (7.9)	1 (1)	
DOD	15 (39.5)	12 (8)	

Outcomes	non-MDA (n=26) n (%)	MDA (n=12) n (%)	P value*
NED	13 (50)	6 (50)	0.66
AWD	3 (12)	0 (0)	
DOD	10 (38)	6 (50)	

*
2-sided exact

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Table 4

Past medical history (PMH) of GAS patients

PMH	n	%
None	33	82.5%
Peutz-Jeghers syndrome	1	2.5%
Li-Fraumeni syndrome with breast cancer	1	2.5%
Breast cancer	2	5.0%
Colon cancer	1	2.5%
Wilms + pheochromocytoma + renal cell carcinoma	1	2.5%
Mucinous BAC lung (KRAS mutation)	1	2.5%

Table 5

Disease stage distribution at presentation

Stage	GAS (n=39)		UEA (n=139)		P value*
	n (%)	%	n (%)	%	
IA1	1 (3)	41	4 (3)	89	<0.001
IA2	1 (3)		18 (13)		
IB1	13 (33)		95 (68)		
IB2	1 (3)		7 (5)		
IIA	6 (15)	59	6 (4)	11	
IIB	2 (5)		3 (2)		
IIIA	2 (5)		0 (0)		
IIIB	7 (18)		5 (4)		
IVB	6 (15)		1 (1)		

Stage	non-MDA (n=26)		MDA (n=13)		P value*
	n (%)	%	n (%)	%	
IA1	1 (3)	31	0 (0)	62	0.091
IA2	0 (0)		1 (3)		
IB1	6 (15)		7 (18)		
IB2	1 (3)		0 (0)		
IIA	4 (10)	69	2 (5)	38	
IIB	2 (5)		0 (0)		
IIIA	2 (5)		0 (0)		
IIIB	7 (18)		0 (0)		
IVB	3 (8)		3 (8)		

*
2-sided exact

Table 6

Additional routinely assessed pathologic variables at presentation.

Pathologic Findings	GAS n (%)	UEA n (%)	P value*
Lymphovascular invasion	11/23 (48)	21/158 (13)	<0.001
Regional LN metastasis	9/18 (50)	12/158 (8)	<0.001
Remote LN metastasis	4/18 (22)	1/158 (1)	<0.001
Ovarian metastasis	8/23 (35)	0/158 (0)	<0.001
Other pelvic organ(s) involvement	9/25 (36)	2/158 (1)	<0.001
Abdominal spread	5/25 (20)	1/158 (1)	<0.001

Pathologic Findings	non-MDA n (%)	MDA n (%)	P value*
Lymphovascular invasion	8/13 (62)	3/10 (30)	0.21
Regional LN metastasis	9/15 (60)	0/3 (0)	0.21
Remote LN metastasis	4/15 (27)	0/3 (0)	1.00
Ovarian metastasis	5/13 (38)	3/10 (30)	1.00
Other pelvic organ(s) involvement	7/14 (50)	2/11 (18)	0.21
Abdominal spread	3/14 (21)	2/11 (18)	1.00

*
2-sided exact

Table 7A

Disease specific survival information (GAS vs. UEA).

DSS	GAS (n=38)						UEA (n=139)						P value
	5 year			10 year			5 year			10 year			
	survival (%)	SE (%)		survival (%)	SE (%)		survival (%)	SE (%)		survival (%)	SE (%)		
All stages	42	11.5		31	12.5		91	2.9		81	5.6		<0.0001
Stage I only	62	16.6		62	16.6		96	2.5		93	3.7		0.0003

SE = Standard error

Table 7B

Disease specific survival information (MDA vs. non-MDA subtypes).

DSS	MDA (n=12)			non-MDA (n=26)				P value
	5 year		10 year	5 year		10 year		
	survival	SE		survival	SE	survival	SE	
	0.00	--	0.00	--	0.48	0.135	0.36	
All stages								0.36

DSS - disease specific survival; SE - standard error

Table 8

Summary of disease recurrence

	GAS (n=37) n (%)	UEA (n=139) n (%)	P value*
Recurrences			
Yes	12 (32)	6 (4)	<0.001
No	25 (68)	152 (96)	
Time to recurrence (mo)			
Mean (range)	9 (2-22)	23 (1-67)	<0.001
Site of recurrence			
Vagina/pelvis	7	2	0.62
Abdomen (peritoneum, omentum, bowel)	5	0	0.11
Retroperitoneum	1	0	1.00
Pelvic lymph nodes	2	0	0.53
Bone	1	0	1.00
Liver	1	1	1.00
Lung	1	3	0.08
Brain	1	0	1.00

	non-MDA (n=25) n (%)	MDA (n=12) n (%)	P value*
Recurrences			
Yes	6 (24)	6 (50)	0.14
No	19 (76)	6 (50)	
Time to recurrence (mo)			
Mean (range)	10 (3-22)	9 (2-22)	0.79

Site of recurrence			
Vagina/pelvis	3	4	1.00
Abdomen (peritoneum, omentum, bowel)	1	4	0.24
Retroperitoneum	1	0	1.00
Pelvic lymph nodes	2	0	0.45
Bone	1	0	1.00
Liver	1	0	1.00
Lung	1	0	1.00
Brain	1	0	1.00

* 2-sided exact; bone and brain metastasis in one patient, liver and lung met in another patient

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Table 9

Comparison of GAS vs UEA

	Gastric type adenocarcinoma	Usual endocervical adenocarcinoma
Precursor lesions	Lobular endocervical glandular hyperplasia	Adenocarcinoma in-situ
Location	Upper endocervical canal	Transformation zone
HPV associated	No	Yes
P16 immunohistochemistry	Negative or focal	Diffusely positive
Presentation	Often at high stage	Uncommonly high stage