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Analysis of gastric-type mucinous carcinoma of the uterine cervix — An aggressive tumor with a poor prognosis: A multi-institutional study☆

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HIGHLIGHTS

- GAS showed aggressive behavior with ominous histopathological predictors as well as decreased survival.
- GAS also showed resistance to radiotherapy.
- GAS is therefore considered a distinct entity that should be distinguished from UEA.

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ABSTRACT

Objective. Gastric-type mucinous carcinoma (GAS) is a novel variant of mucinous carcinoma of the uterine cervix. As shown in the original Japanese group description, in recent studies, GAS represents a more aggressive disease than the usual-type endocervical adenocarcinoma (UEA). Detailed clinicopathological features of this variant remain to be elucidated in a larger series of patients.

Methods. Patients were enrolled by the Gynecologic Cancer Study Group of the Japan Clinical Oncology Group after receiving the approval of each Institutional Review Board. The study population comprised of women with stage I to II endocervical adenocarcinomas who underwent surgery between 2000 and 2009. Representative slides were evaluated by central pathological review (CPR), categorized into either GAS or UEA, and correlated with clinicopathological features and outcome.

Results. Among the 393 enrolled patients with endocervical adenocarcinoma, 328 patients met the criteria for CPR and the study eligibility criteria and were included in further analysis. A total of 95 of the 328 tumors were classified as GAS. Compared with UEA, GAS was more significantly associated with bulky mass, deep stromal invasion, lymphovascular space invasion, parametrial invasion, ovarian metastasis, positive ascitic fluid cytology,

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pelvic lymph node metastasis, and pathological (p) T stage but was not related to the degree of histological differentiation. Disease-free survival ($P < 0.0001$) and overall survival ($P < 0.0001$) were poorer in patients with GAS than in those with UEA.

Conclusions. GAS showed aggressive behavior with ominous histopathological predictors as well as decreased survival. GAS is therefore considered a distinct entity that should be distinguished from UEA.

Clinical trial information. UMIN Clinical Trials Registry: UMIN000007987

1. Introduction

Uterine cervical cancer is the third most common cancer in women, with 528,000 new cases diagnosed each year, and it accounts for 266,000 annual deaths worldwide [1]. During the past decade, the prevalence of adenocarcinoma of the uterine cervix increased from approximately 5% to 20% of cervical cancers [2]. Recently, a number of authors have reported that the 5-year overall survival rate is 10% to 20% lower in nonsquamous cell carcinoma (non-SCC) than in SCC [3,4]. Additionally, recent studies have provided evidence that adenocarcinoma clearly differs from SCC with respect to its molecular pathogenesis [5,6]. Therefore, it was suggested that the histological type should be considered when deciding on treatments for patients with cervical cancer [2,7]. Otherwise, adenocarcinomas of the cervix are related to persistent high-risk human papillomavirus (HPV) infection [8–11].

However, there is an emerging spectrum of non–HPV-related cervical adenocarcinomas. For example, in a recent large European study with centralized pathology review and sensitive HPV detection methods, high-risk HPV was detected in over 90% of usual-type adenocarcinomas (UEA), whereas the detection rates were much lower in other morphologic variants; for example, 28% was reported in clear cell carcinomas [12]. It has become clear recently that the most common variant of non-HPV-related cervical adenocarcinoma belongs to a spectrum of adenocarcinomas.

Gastric-type mucinous carcinoma (GAS) of the uterine cervix is a relatively newly recognized variant of endocervical adenocarcinoma. GAS was initially described by Japanese groups [14–16] and was included as a subtype of endocervical mucinous adenocarcinoma in the World Health Organization (WHO) classification updated in 2014 [17]. It is defined as a mucinous carcinoma with gastric-type differentiation and includes minimal deviation adenocarcinoma (MDA), also known as adenoma malignum because of its morphologic spectrum [17]. In contrast to UEA, GAS is frequently located in the upper endocervix and shows a bulky cervix without a well-demarcated mass because of its highly infiltrating pattern of growth [18]. Whereas most UEAs are HPV-related, GAS is reported to be unrelated to HPV and is importantly associated with an aggressive clinical behavior, resulting in poorer outcomes than those of UEA [8,9,16,19,20]. Although GAS is considered rare in Western countries [12], it is rather common in Japan, accounting for up to 20% to 25% of all endocervical adenocarcinomas [16,19]. Therefore, the discrepancies in the data used to determine the outcomes in patients with endocervical adenocarcinoma might reflect differences in the incidences of GAS reported in each study.

A Japanese group reported that GAS represents more aggressive disease than does UEA [21]. However, this remains to be confirmed in a larger series of patients. Here we examine whether GAS represents a more aggressive disease than does UEA in a larger series.

2. Methods

Patients were enrolled by the Gynecologic Cancer Study Group of the Japan Clinical Oncology Group (JCOG-GCSG) after receiving approval from each Institutional Review Board (study ID designated as UMIN000007987 by the UMIN Clinical Trials Registry). The study population comprised of women with stage I to II disease who underwent surgery without receiving neoadjuvant chemotherapy between 2000 and 2009.

All patients underwent radical hysterectomy with pelvic lymphadenectomy or para-aortic lymph-node biopsy, or both. The pelvic lymph node dissection included bilateral removal of the external iliac (suprainguinal), internal iliac, obturator, and common iliac lymph nodes. Para-aortic lymph-node biopsy was performed from the aortic bifurcation to the level of the renal vessels. Patients with deep stromal invasion, lymphovascular invasion, parametrial invasion, and lymph node metastases were administered adjuvant therapy. After surgery, 131 patients (197 patients did not) received post-operative adjuvant therapy. External beam radiotherapy was performed with 50.4 Gy to the entire pelvis. Intracavitary brachytherapy was performed if the surgical margin of the vaginal cuff was involved histologically or if the free margin measured <1 cm.

Representative glass slides of all cases were evaluated by central pathological review (CPR) on the basis of the current WHO classification updated in 2014 to determine the differences in the clinicopathological features between GAS and UEA. Additionally, the outcomes in patients with each type of disease were statistically compared. In a CPR of hysterectomy specimens, two of the authors (Y.M. and T.K.), who are board-certified pathologists specializing in gynecological pathology and oncology, reviewed representative glass slides, without providing them with any clinical information or the original histopathological diagnosis. Morphologically, GAS was defined as mucinous carcinoma showing (i) clear or pale eosinophilic cytoplasm, (ii) voluminous cytoplasm, and (iii) distinct cell borders, whereas UEA was defined as mucin-deficient or mucin-poor carcinoma that does not meet the criteria for any other subtype of endocervical adenocarcinoma. All relevant pathological and clinical data were collected and analyzed.

2.1. Statistical analysis

The statistical significance of differences in the proportions of cases within each histologic group having various pathologic or clinical features was assessed using Fisher's exact test [22]. The survival time of each patient was calculated from the date of diagnosis to date of death, with right-censoring at the date of the last follow-up for 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 Kaplan-Meier method [23]. The log-rank test was used to compare two survival curves [24,25].

P-values of <0.05 indicate statistical significance, unless otherwise stated. For survival analysis, data on overall survival (OS) were censored from the date of surgery to the date of the last follow-up; events were defined as death from any cause. Data on progression-free survival (PFS) were censored from the date of surgery to the date of the last follow-up if disease progression had not occurred; events were defined as death from any cause, disease relapse, and disease progression. All reported *P*-values are two-sided. Statistical analysis was performed with SAS, version 9.1 (SAS Institute, Inc., Cary, NC) and revised version 2.7.0.

2.2. HPV studies

Paraffin-embedded tissue samples were cut at a thickness of 10 μm and placed on coated glass slides. HPV testing was performed in 31

GAS cases. In all cases, linear array HPV genotyping (Roche Molecular Diagnostics, Pleasanton, CA) was performed. The Roche linear array HPV genotyping test involves polymerase chain reaction amplification of target DNA followed by hybridization for the detection of 37 HPV types, including 18 high-risk types (16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, 82) and 19 low-risk types (6, 11, 40, 42, 54, 55, 61, 62, 64, 67, 69, 70, 71, 72, 81, 83, 84, IS39, CP108).

3. Results

A total of 393 patients with endocervical adenocarcinoma were enrolled in our project. Sixty-five patients were ineligible for this study according to CPR or because of insufficient or wrong clinical information (25 patients had stage III or IV disease, and 40 patients had the following histologic types: lobular endocervical glandular hyperplasia [LEGH] in 5 patients, adenocarcinoma in situ (AIS) in 18 patients, endometrioid carcinoma in 10 patients, undifferentiated carcinoma in 5 patients, and serous carcinoma in 5 patients). Thus, 328 patients with endocervical adenocarcinomas were included in this study, and of the tumors, 95 (28.9%) were re-classified as GAS. The patients' characteristics are shown in Table 1. The median age of the patients was 45 years (range: 21–79). The median tumor marker level was 15 U/mL (range: 0.6–900.3) for CA125, 13 U/mL (range: 0.1–5850.2) for CA19–9, and 1.6 ng/mL (range: 0.2–351.3) for CEA. The median tumor diameter was 20 mm (range: 2–64.1). The pathological T stage and the degree of differentiation are shown in Table 1. Among the 131 patients who received postoperative adjuvant therapy (197 patients [60.1%] did not), radiotherapy, concurrent chemoradiotherapy, chemotherapy, and chemotherapy plus radiotherapy, were administered to 41 (12.5%), 22 (6.7%), 66 (20.1%), and 2 (0.6%) patients, respectively.

Compared with UEA, GAS was significantly associated with tumor diameter of <40 mm (bulky mass), deep stromal invasion, lymphovascular invasion, parametrial invasion, ovarian metastasis, positive ascitic cytology, pelvic lymph node metastasis, and pT factor, but there was no correlation with tumor differentiation (Table 2). The results of Kaplan–Meier analysis are shown in Fig. 2. The median PFS was 61.1 months in patients with UEA and 42 months in patients with GAS. PFS and OS were poorer in patients with GAS than in patients with UEA (Fig. 1).

Table 3 shows the results from the univariate and multivariate Cox regression models, respectively. Variables significantly associated in the univariate analysis with PFS and OS included, tumor diameter (≥40 mm vs. <40 mm; hazard ratio [HR] 3.408, 95% CI, 1.705–6.812; $P = 0.0005$ and 4.3, 95% CI, 1.942–9.522; $P = 0.0003$, respectively), parametrial invasion (present vs. absent; HR 3.012, 95% CI, 1.112–8.658; $P = 0.0306$ and 4.577, 95% CI, 1.338–15.66; $P = 0.0154$, respectively), differentiation (poorly differentiated vs. moderately and well differentiated; HR 3.228, 95% CI, 1.771–5.884; $P = 0.0001$ and 2.978, 95% CI, 1.499–5.918; $P = 0.0018$, respectively), ovarian metastasis (present vs. absent; HR 19.014, 95% CI, 4.582–78.894; $P < 0.0001$ and 18.362, 95% CI, 3.684–91.526; $P = 0.0004$, respectively), and GAS (present vs. absent; HR 2.365, 95% CI, 1.287–4.347; $P = 0.0056$ and 2.984, 95% CI, 1.485–5.996; $P = 0.0021$, respectively). In contrast, pT stage, stromal invasion, lymph node metastasis, and ascites cytology positive had no effect on survival.

Variables significantly associated in the multivariable analysis with PFS and OS included tumor diameter (≥40 mm vs. <40 mm; HR 3.406, 95% CI, 1.824–6.3612; $P = 0.0001$ and 4.378, 95% CI, 2.105–9.107; $P < 0.0001$, respectively), parametrial invasion (present vs. absent; HR 3.461, 95% CI, 1.864–6.428; $P < 0.0001$ and 2.885, 95% CI, 1.416–5.879; $P = 0.0035$, respectively), lymph node metastasis (present vs. absent; HR 2.286, 95% CI, 1.262–4.14; $P = 0.0064$ and 2.48, 95% CI, 1.269–4.847; $P = 0.0079$, respectively), differentiation (poorly differentiated vs. moderately and well differentiated; HR 3.031, 95% CI, 1.665–5.515; $P = 0.0003$ and 3.057, 95% CI, 1.535–6.09; $P = 0.0015$, respectively), ovarian metastasis (present vs. absent; HR

Table 1
Patient characteristics ($n = 328$).

Factor	N (%)
Age (range)	45 (21–79)
FIGO Stage (1988)	
IA	19 (5.8)
IB1	224 (68.3)
IB2	44 (13.4)
IIA	9 (2.7)
IIB	32 (7.8)
Tumor marker median (range)	
CA125 (U/mL)	15 (0.6–900.3)
CA19-9 (U/mL)	13 (0.1–5850.2)
CEA (ng/mL)	1.6 (0.2–351.3)
Tumor diameter (mm) median (range)	20 (2–64.1)
pT Stage	
Ia	22 (6.7)
Ib1	198 (60.4)
Ib2	43 (13.1)
IIa	22 (6.7)
IIb	43 (13.1)
Differentiation	
Well	233 (71)
Moderately	48 (14.6)
Poorly	17 (4.3)
Unclassified	40 (10.1)
Adjuvant therapy	
None	197 (60.1)
Radiotherapy	41 (12.5)
Concurrent chemoradiotherapy	22 (6.7)
Chemotherapy	66 (20.1)
Chemotherapy + Radiotherapy	2 (0.6)

FIGO, International Federation of Gynecology and Obstetrics; CA 125, cancer antigen 125; CA19-9, carbohydrate antigen 19-9; serum carcinoembryonic antigen (CEA).

Table 2
Comparison of clinicopathological factors between GAS and UEA.

Factor	Histology		P-value
	GAS	UEA	
pT Stage			$P < 0.0001$
Ia	4	18	
Ib1	33	165	
Ib2	22	21	
IIa	12	10	
IIb	24	19	
Tumor diameter			$P < 0.0001$
<40 mm	50	189	
≥40 mm	45	44	
Stromal invasion			$P < 0.0001$
<2/3	38	183	
≥2/3	57	50	
Lymphovascular space invasion			$P < 0.0001$
Present	63	71	
Absent	32	162	
Parametrial invasion			$P < 0.0001$
Present	25	17	
Absent	70	216	
Lymph node metastasis[a]			$P < 0.0001$
Present	33	33	
Absent	57	192	
Differentiation[a]			$P = 0.2716$
Well	66	167	
Moderate, Poorly	23	42	
Ovary metastasis			$P = 0.0481$
Present	5	3	
Absent	90	230	
Ascites cytology[a]			$P = 0.0136$
Positive	10	8	
Negative	77	197	

GAS, gastric-type mucinous carcinoma; UEA, usual-type endocervical adenocarcinoma.
[a] Including missing data.

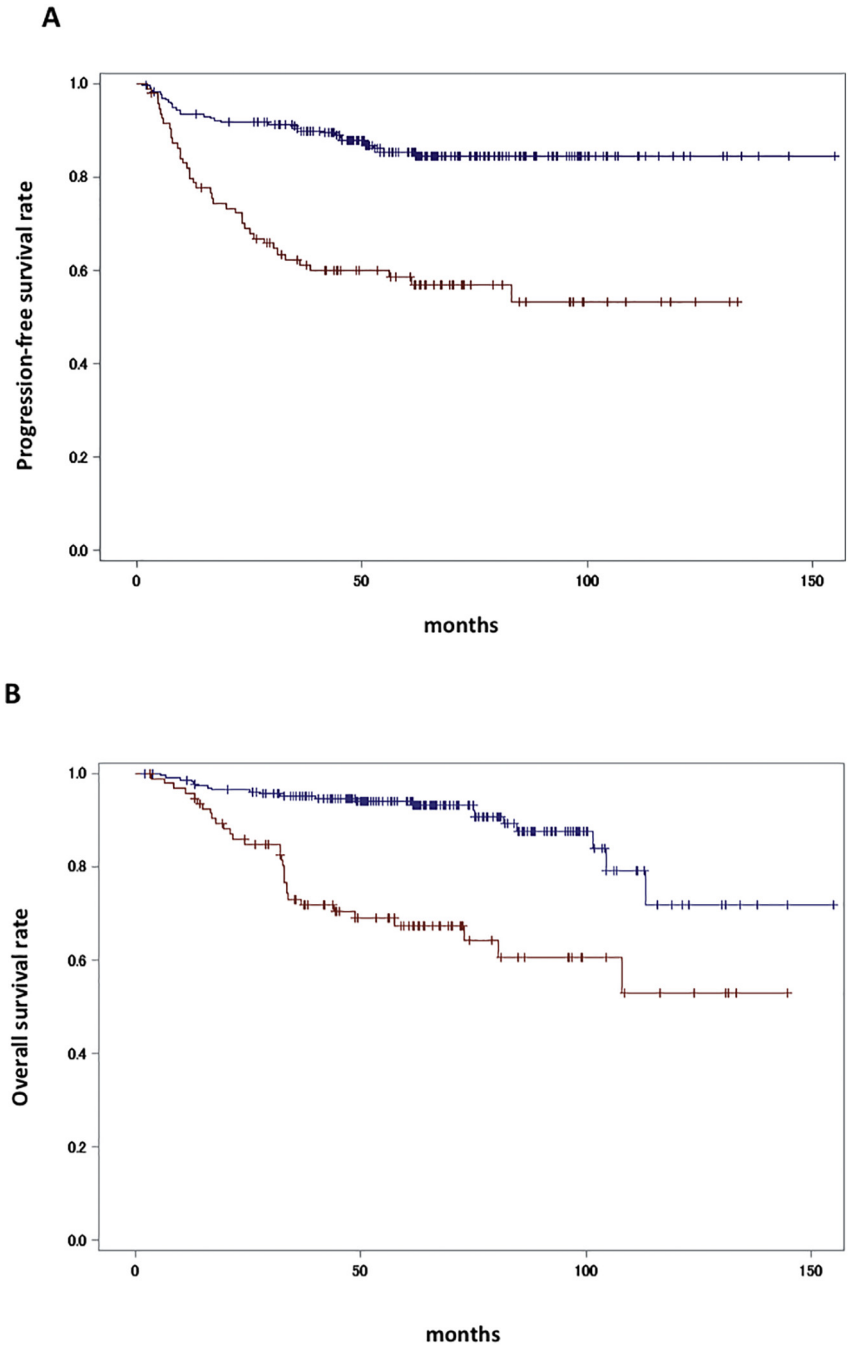

Fig. 1. Progression-free survival and overall survival: blue line, UEA group; red line, GAS group.

9.173, 95% CI, 3.349–25.123; $P < 0.0001$ and 12.178, 95% CI, 4.178–35.494; $P < 0.0001$, respectively), and GAS (present vs. absent; HR 2.361, 95% CI, 1.333–4.182; $P = 0.0032$ and 3.034, 95% CI, 1.566–5.877; $P = 0.001$, respectively).

When stratified according to stage, patients with pT1a-pT1b1 adenocarcinoma had poorer outcomes, but the difference between groups with pT1b2 or more was not significant (Fig. 2A, B).

3.1. HPV results

Linear array HPV genotyping was negative in the 31 patients in whom it was performed.

3.2. Recurrence course

Overall, recurrence occurred in 72 of the 328 patients: 38 (40%) of 95 patients with GAS and 34 (14.6%) of 233 patients with UEA. Recurrence was clearly more common among patients with GAS ($P = 0.0023$). In the GAS group, the sites of recurrence were local in 15 patients, distant in 15, and local plus distant in 8. In the UEA group, the sites of recurrence were local in 19 patients, distant in 11, and local plus distant in 4, with no significant difference between the groups (Table 4). Following recurrence, chemotherapy was administered to 19 patients with GAS, with a response rate of 36.8% (7/19), and to 25 patients with UEA, with a response rate of 32.0% (8/25). The difference in the response rates was not significant.

Table 3
The effect on survival by univariate(A) analysis and multivariate(B) analysis.

Factor	*P*-value		Hazard Ratio		95% CI	
	PFS	OS	PFS	OS	PFS	OS
A						
pT stage	$P = 0.5947$	$P = 0.3366$	1.294	0.562	0.501–3.341	0.164–1.82
Tumor diameter	$P = 0.0005$	$P = 0.0003$	3.408	4.3	1.705–6.812	1.942–9.522
Stromal invasion	$P = 0.2651$	$P = 0.6162$	1.618	1.275	0.694–3.772	0.493–3.298
Lymph vascular space invasion	$P = 0.3039$	$P = 0.8944$	0.09	1.055	0.34–1.4	0.476–2.343
Parametrial invasion	$P = 0.0306$	$P = 0.0154$	3.102	4.577	1.112–8.658	1.338–15.66
Lymph node metastasis	$P = 0.0507$	$P = 0.033$	1.932	2.24	0.998–3.739	1.067–4.699
Differentiation	$P = 0.0001$	$P = 0.0018$	3.228	2.978	1.771–5.884	1.499–5.918
Ovary metastasis	$P < 0.0001$	$P = 0.0004$	19.014	18.362	4.582–78.894	3.684–91.526
Ascites cytology	$P = 0.1633$	$P = 0.8607$	0.458	0.897	0.153–1.373	0.266–3.025
GAS	$P = 0.0056$	$P = 0.0021$	2.365	2.984	1.287–4.347	1.485–5.996
B						
Tumor diameter	$P = 0.0001$	$P < 0.0001$	3.406	4.378	1.824–6.361	2.105–9.107
Parametrial invasion	$P < 0.0001$	$P = 0.0035$	3.461	2.885	1.864–6.428	1.416–5.879
Lymph node metastasis	$P = 0.0064$	$P = 0.0079$	2.286	2.48	1.262–4.14	1.269–4.847
Differentiation	$P = 0.0003$	$P = 0.0015$	3.031	3.057	1.665–5.515	1.535–6.09
Ovary metastasis	$P < 0.0001$	$P < 0.0001$	9.173	12.178	3.349–25.123	4.178–35.494
GAS	$P = 0.0032$	$P = 0.001$	2.361	3.034	1.333–4.182	1.566–5.877

CI, confidence interval; PFS, progression-free survival; OS, overall survival; GAS, gastric-type mucinous carcinoma.

Radiotherapy was administered to 12 patients with GAS, with a response rate of 50.0% (6/12), and to 11 patients with UEA, with a response rate of 81.8% (9/11, $P < 0.0001$). GAS was thus significantly more resistant to radiotherapy.

4. Discussion

Currently, endocervical adenocarcinoma is considered to be a heterogeneous group of tumors showing significant clinical, etiologic, and morphologic diversity, and the implication of high-risk HPV has become a crucial issue [26,27]. In the 2014 WHO classification, mucinous adenocarcinoma was distinguished from UEA and included gastric, intestinal, and signet ring-cell types, whereas MDA was regarded as the highly differentiated form of GAS [17]. Our work and that of other investigators support the conclusion that GAS constitutes a unique tumor type with distinct etiologic, morphologic, and clinical features that set it apart from other mucinous carcinomas [8,9,11,16,19]. This present work confirms the conclusion offered by Kojima et al. [16] and builds on it. GAS is a clinically aggressive neoplasm with a distinctive histologic appearance. To our knowledge, our study of 328 patients with mucinous endocervical adenocarcinoma, including 95 patients with a diagnosis of GAS, is the largest study of its type in the world.

Karamurzin et al. [20] showed that GAS typically presents at a more advanced stage than HPV-associated UEA, and survival analysis restricted to patients with International Federation of Gynecology and Obstetrics (FIGO) stage I tumors indicated that GAS remained more aggressive. In our study, the proportion of patients with GAS markedly increased as the disease stage progressed (Table 2). However, although GAS was associated with poorer outcomes than those of UEA in patients with Ia-Ib1-stage disease, there was no difference in outcomes in patients with Ib2-II-stage disease (Fig. 2A, B). This finding suggests that GAS might be associated with poorer outcomes among patients with early-stage cancer.

Our study clearly shows that recurrence was more common among patients with GAS ($P = 0.0023$). In the GAS group, the sites of recurrence were local in 15 patients, distant in 15, and local plus distant in 8. In the UEA group, the sites of recurrence were local in 19 patients, distant in 11, and local plus distant in 4, with no significant difference between the groups. In a previous study, there was also no difference in the sites of recurrence between GAS and UEA [20].

The diagnosis of GAS is established primarily based on morphology; among pathologists, reproducibility is confirmed to be optimal according to their familiarity with the histopathological criteria of GAS [28]. However, immunohistochemistry may contribute to the establishment of the diagnosis, particularly in cases of small biopsy specimen. GAS typically shows the gastric phenotype, as demonstrated by HIK1083, MUC6, or carbonic anhydrase type IX staining, and is negative for p16. Additionally, it frequently shows a mutant pattern of p53 staining [29]. Although we did not perform immunohistochemical analysis in our study, the concordance rate of the central pathological evaluation by the expert panel was 98.9% (94/95), suggesting that ancillary studies might not always be required for the diagnosis of GAS. On the other hand, the results of HPV DNA tests were negative in all 31 patients in whom such examinations were performed, suggesting that HPV tests may be useful for the diagnosis of GAS.

The results of our multivariable analysis showed that along with GAS, the following factors were also predictors of the outcomes: tumor diameter ≥40 mm, parametrial invasion, lymph node metastasis, poorly differentiated cancer, and ovarian metastasis.

Since the first description of GAS in 2007, some authors have reported its poorer outcomes than those of UEA in retrospective studies [16,26]. However, the cause of its aggressive behavior remained unknown; possibilities such as difficulty in early detection, chemoresistance, and radioresistance were considered. Kojima et al. [21] showed significant differences in chemosensitivity and survival outcomes between UEA and GAS in patients for whom chemotherapy regimens had been strategically selected and who were prospectively followed up in a phase 2 study.

Among patients who had recurrence in our study, radiotherapy was administered to 12 patients with GAS, with a response rate of 50.0% (6/12), and to 11 patients with UEA, with a response rate of 81.8% (9/11, $P < 0.0001$). GAS was thus significantly more resistant to radiotherapy. Such resistance to chemotherapy and radiotherapy might contribute to the poorer outcomes in GAS.

Recently, a large comprehensive genomic study of 228 patients with cervical cancer reported that patients with endometrial-like cervical cancers, which mainly comprised HPV-negative tumors, had relatively high frequencies of KRAS, ARID1A, and PTEN mutations [30]. Such molecular analyses may lead to a breakthrough,

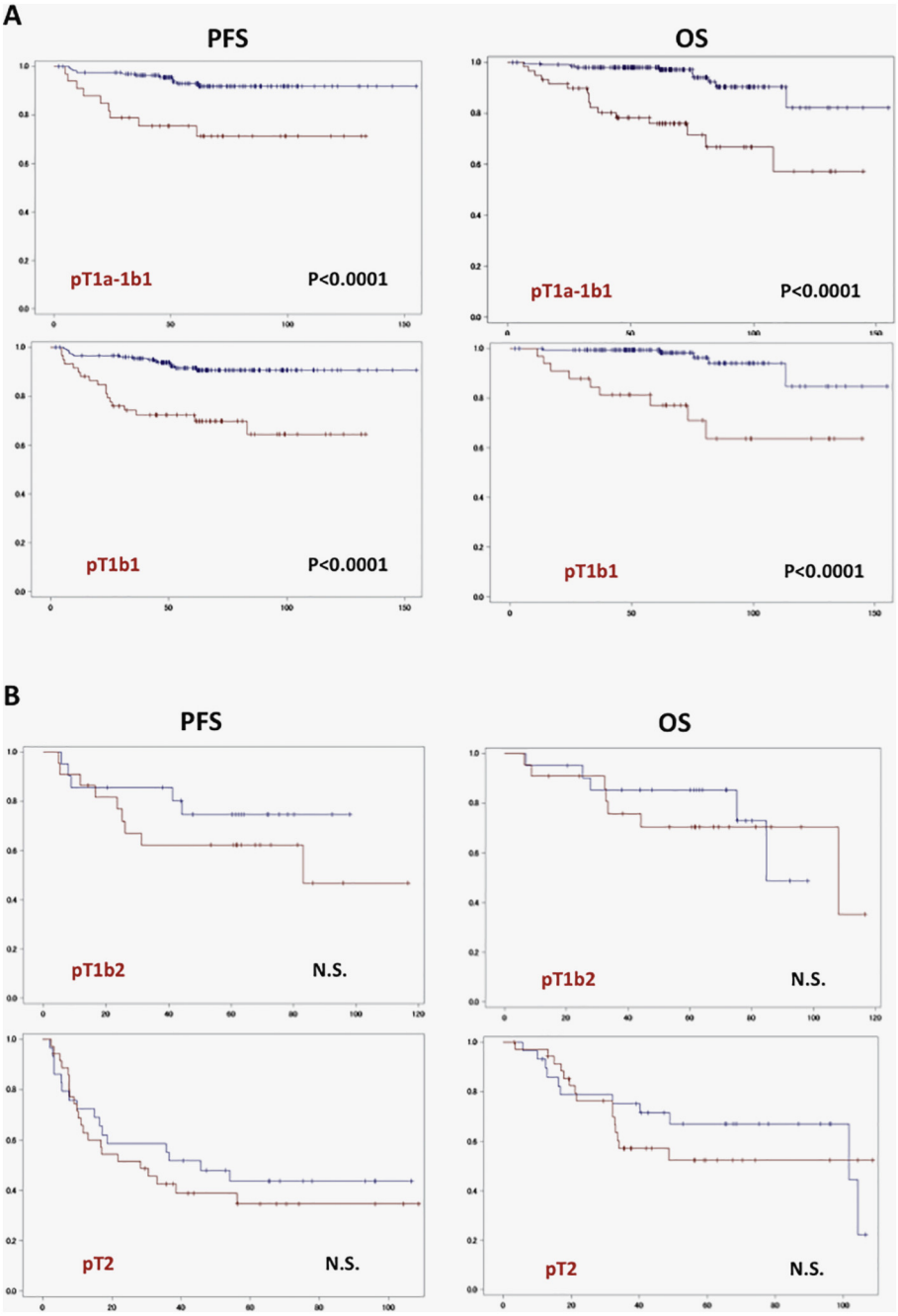

Fig. 2. A: Survival curve of patients with pT1a-1b1 and pT1b1: PFS, progression-free survival; overall survival; blue line, UEA group; red line, GAS group. B: Survival curve of patients with pT1b2 and pT2: blue line, UEA group; red line, GAS group; N.S., not significant.

revealing new potential therapeutic targets for lethal cervical cancer, such as GAS.

To achieve better oncologic outcomes in patients with locally advanced, aggressive types of cervical cancer such as GAS, various multidisciplinary treatment strategies incorporating cisplatin-based concurrent chemoradiotherapy and molecular targeted therapy have been evaluated. However, the profiles of the genomic signatures of unusual cervical cancers, represented by GAS as well as clear cell carcinoma and serous carcinoma, are still limited, and definitive treatment guidelines for such cancers remain to be established.

In conclusion, GAS is significantly associated with histopathological predictors of poor outcomes as well as with poorer survival outcomes and is therefore considered a distinct entity that should be distinguished from UEA. Further research needs to elucidate molecular mechanism and genomic study for GAS.

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Disclosure

The authors have declared no conflict of interest.

Table 4
Sites of recurrence[a] ($n = 72$).

Site	GAS	UEA
Brain	1	0
Lung	10	9
Liver	2	3
Peritoneum	3	1
Bone	2	0
Abdominal lymph node	6	9
Pelvic lymph node	6	7
Pelvis	8	5
Vaginal cuff	10	9
Local site	15	11
Distant site	15	19
Local site + Distant site	8	4

GAS, gastric-type mucinous carcinoma; UEA, usual-type endocervical adenocarcinoma.
[a] Duplicated cases included.

Author contributions

All authors contributed to study design, data interpretation and writing. Data analysis was primary performed by SN.

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