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Original Article

Clinicopathologic characteristics and outcome of gastric-type endocervical adenocarcinoma: a single-center retrospective study

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Abstract: Background: This study investigated the clinical and pathological characteristics of gastric-type endocervical adenocarcinoma (G-EAC) to advance the early diagnosis and treatment of this disease. Methods: The diagnosis, treatment, follow-up, pathological morphology, immunohistochemical characteristics and other data of 15 patients of G-EAC visiting our hospital from December 2016 to March 2024 were retrospectively analyzed, and the relevant literature was discussed. Results: The mean age of participants was 45.13 years. There were four cases with vaginal discharge, eight cases with spontaneous vaginal contact bleeding, one case where hysterosalpingography (HSG) demonstrated uterine cavity fluid accumulation, and two cases of abdominal pain and swelling with pelvic mass (one with fever) as the initial symptom. There were two participants with Peutz-Jeghers syndrome (PJS). Histologically speaking, G-EAC exhibited various morphologic characteristics, including well-differentiated glands and unusual glands dispersed randomly within the cervical stroma and lacking lobular structures. Neutrophil infiltration and glandular abscess formation were commonly observed. Immunohistochemical analysis showed no expression of ER, PR, or NapsinA, but varying degrees of CK7, MUC6, MUC5AC, CEA, HNF1β, and PAX-8 expression. During the follow-up, which lasted from 1 to 88 months, 2 participants died after 6 months and 10 months respectively. Moreover, 5 participants exhibited distant metastasis, and the remaining 8 participants were healthy and disease free. Conclusion: G-EAC is an uncommon subtype of cervical adenocarcinoma that frequently manifests as an advanced-stage cancer with vague clinical symptoms, making biopsy-based diagnosis challenging. Since conventional treatments demonstrated limited efficacy, clinicians and pathologists should pay particular attention to this entity.

Keywords: Diagnosis, endocervical adenocarcinomas, gastric-type adenocarcinoma, Peutz-Jeghers syndrome (PJS), prognosis

Introduction

Cervical carcinoma is the most common gynecological malignancy in underdeveloped countries. Approximately 90% of cervical carcinomas are squamous cell carcinoma (SCC), while the remaining cases are adenocarcinomas [1]. During the past decade, the fraction of adenocarcinoma of the cervix increased from approximately 5% to 20% of cervical cancers. Unlike cervical SCC, which is caused by HPV, adenocarcinomas of the cervix represent a much more heterogeneous group of tumors, with approximately 15% being unrelated to HPV infection [2]. According to the 2020 WHO classification of tumors of the female reproductive system, gastric-type endocervical adenocarcinoma (G-EAC) is the most prevalent type of human papillomavirus (HPV)-independent adenocarcinoma with the worst prognosis. Kojima *et al*. (2007) reported that it is difficult to diagnose G-EAC based on biopsy because the lesion is hidden [3], making it more prone to misdiagnosis compared to HPV-associated endocervical adenocarcinoma and SCC [4]. This study retrospectively reviewed 15 cases of G-EAC, highlighting its unique morphology, immunochemical features, treatment, and follow-

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Figure 1. Case 2 exhibits black spots on the fingertips.

up to verify whether G-EAC is more aggressive than usual-type endocervical adenocarcinoma (UEA).

Materials and methods

Materials

Cervical adenocarcinomas were consecutively searched using the keywords "cervical/endocervical adenocarcinoma, the type of human papillomavirus (HPV)-independent" in the computer system from the in-house files of the Department of Pathology, Anyang Tumor Hospital (Henan Province, China) between December 2016 and March 2024. Additional keywords such as "gastric-type" were used to identify G-EAC. The clinical data, including clinical presentation and treatment, were extracted from the electronic medical records before de-identification. Two authors (H.L. and R.L.) independently reviewed full archival hematoxylin and eosin (H&E) slides (median 18, range: 14-38 slides per case) of all G-EAC for detailed morphological analysis and reclassification following the International Endocervical Adenocarcinoma Criteria and Classification (IECC) [4]. The tumor stage was reassessed based on the 2018 International Federation of Gynecology and Obstetrics (FIGO) cervical cancer staging system [5]. Complete clinicopathological and follow-up data were obtained from the records or through telephone calls. The deadline for follow-up was April 20, 2024.

Methods

All of the surgical specimens were fixed in 3.7% formalin, embedded routinely in paraffin, and stained with hematoxylin and eosin. Immunohistochemical studies were conducted using commercial antibodies in the Ventana BenchMark ULTRA instrument (Basel, Switzerland). Pre-diluted antibodies against the following proteins were used: MUC6, MUC5AC, MUC2, CK7, CEA, P16, P53, PAX2, HNF1β (Maixin, FuZhou, China), PAX8, NapsinA (Zhongshanjinqiao, Beijing, China), ER, PR and Ki-67 (Roche). Positive controls were set up for all IHC tests.

Results

Clinical characteristics

This cohort study was conducted on 15 patients diagnosed with G-EAC. The mean age of participants was 45.13 years (range: 32-69 years). 4 participants had a vaginal discharge, 8 cases had vaginal contact bleeding without inducement, 1 case had hysterosalpingography (HSG) with fluid accumulation in the uterine cavity, and 2 cases had abdominal pain and swelling with pelvic mass (1 of them had fever) as the first symptom. Case 2 reported a history of bowel obstruction and resection of multiple adenomas in the jejunum and ileum, and case 11 concurrently had a transverse colon adenoma. They also had dark spots on the lips and fingertips (**Figure 1**). Additionally, preoperative HPV in situ hybridization testing was conducted on 12 participants, all of whom had negative results. Based on the FIGO classification, 6 participants (40.0%) were in stage I, 5 participants (33.3%) were in stage III, and 4 participants (26.7%) were in stage IV. Preoperative high-risk and low-risk HPV *in situ* hybridization tests were negative in 12 cases. Ten cases underwent total hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymphadenectomy after pre-operative cervical biopsies that revealed adenocarcinoma. A proportion of patients were diagnosed following a second opinion consultation with a specialist pathologist at a tertiary care institution's pathology department). Two patients (case 1 and case 2) were

Table 1. Clinical data of 15 cases of G-EAC

Case	Age (yr)	FIGO stag	Clinical features	HPV test results	Preoperative tumor markers		Surgery	Follow-up (mo)
					CA125 (0-35 IU/ml)	CA199 (0-35 IU/ml)		
1	33	4A	Right lower abdominal pain with nausea, vomiting, abdominal and pelvic effusion	-	52.88	57.77	BSO+AP+OM+PN	ANED (28 mo)
2	33	4B	Intermittent fever, lower abdominal swelling, multiple pelvic space occupying (P-J syndrome, history of intussusception)	-	226.50	ND	R AHBSO+PMR+EJM	DOD (6 mo)
3	32	3C2p	Vaginal discharge	ND	23.40	ND	R AHBSO+PLND+PALND	Bladder recurrence (22 mo); AWD (42 mo)
4	65	1B2	No predisposing vaginal bleeding	-	7.72	10.54	R AHBSO+PLND+OM	Bilateral lung recurrence (11 mo), AWD (27 mo)
5	55	3C1p	Vaginal discharge	-	13.05	76.13	R AHBSO+PLND+PALND	ANED (17 mo)
6	43	4A	Contact-induced vaginal bleeding	-	12.50	ND	CC R AHBSO+PLND	ANED (88 mo)
7	68	1B3	Vaginal irregular bleeding, intra-uterine effusion	-	3.3	6.3	R AHBSO	ANED (13 mo)
8	34	1B3	Vaginal fluid	-	22.40	65.96	R AHBSO+PLND	ANED (8 mo)
9	41	3C1p	Lower abdominal pain for 20 days, discovery of cervical growths	-	64.83	1600.90	HBS+PLND	Bilateral ovarian recurrence (27 mo), AWD (33 mo)
10	35	1B3	Contact-induced vaginal bleeding	ND	10.95	ND	HBS+PLND	Bilateral ovarian recurrence (57 mo), AWD (62 mo)
11	35	1B3	Vaginal discharge	-	3.90	157.49	HLFTO+PLND+OM	lung recurrence (84 mo), AWD (87 mo)
12	39	3C1p	Contact-induced vaginal bleeding	-	37.38	ND	R AHBSO+PLND	ANED (9 mo)
13	61	3C1p	Contact-induced vaginal bleeding	-	7.16	2.70	R AHBSO+PLND	ANED (1 mo)
14	34	4A	Abdominal distension with associated poor appetite, nausea, and vomiting	-	84.78	Greater than 6000	R AHBSO+PLND+OM+AP	ANED (1 mo)
15	69	1B3	Intrauterine fluid	ND	ND	ND	R AHBSO	ANED (1 mo)

ND: not done; AP: appendectomy; OM: omentectomy; BSO: bilateral salpingo-oophorectomy; PN: Peritoneal nodulectomy; R AHBSO: radical abdominal hysterectomy and bilateral salpingo-oophorectomy; PMR: Pelvic mass resection; E JM: Excision of jejunal mass; PLND: pelvic lymph-node dissection; PALND: Paraaortic lymph node dissection; CC: Cervical conization; HBS: hysterectomy and bilateral salpingectomy; HLFTO: Hysterectomy and left fallopian tube oophorectomy; ANED: alive with no evidence of disease; AWD: alive with disease; DOD: died of disease; mo: months.

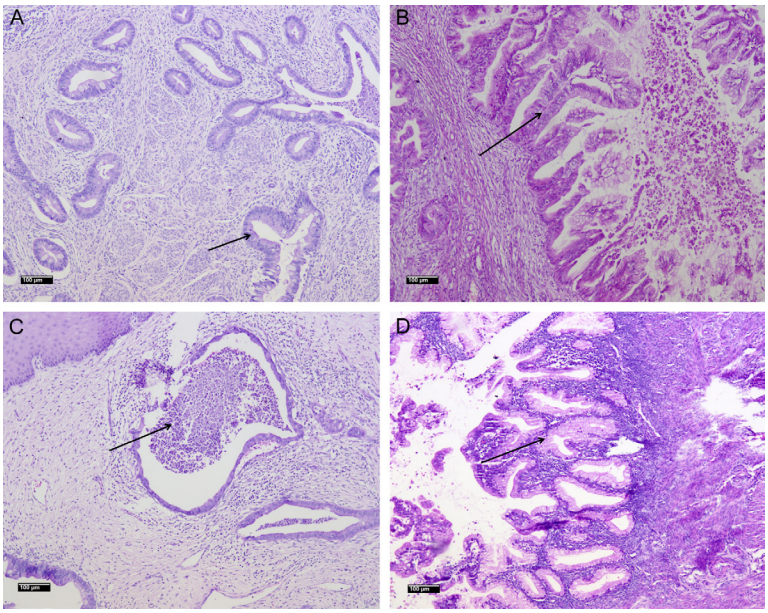

Figure 2. The pathologic characteristics of G-EAC. A: Well-differentiated glands arranged randomly within the cervical canal wall (H&E, 50×, Black arrow mark). B: The glandular cells showed significant atypia, with papillary growth into the cavity (H&E, 100×, Black arrow mark). C: Abscess was seen in the gland cavity (H&E, 100×, Black arrow mark). D: Case 2 had endometrial glandular mucification (H&E, 100×, Black arrow mark).

found to have G-EAC after undergoing ovarian mass resection. Case 15 underwent laparoscopic total hysterectomy and bilateral salpingo-oophorectomy due to intrauterine fluid accumulation, and was incidentally diagnosed with G-EAC. Case 11 (PJS) was diagnosed with ovarian mucinous borderline tumor during cesarean section, and then underwent total hysterectomy, left adnexectomy, pelvic lymph node dissection, and omentectomy, which confirmed G-EAC. **Table 1** summarizes the primary clinical and follow-up data of the 15 participants.

Imaging plays a critical role in the diagnosis of G-EAC. In this study, magnetic resonance imaging (MRI) and PET-CT suggested cervical cancer in 7 participants and one participant, respectively.

Preoperative tumor markers: Among the participants, 9 underwent CA199 testing, 6 of whom had CA199 levels more than the upper limit of normal values, In addition, 14 cases underwent CA125 testing, 4 of whom had CA125 levels more than the upper limit of normal.

The follow-up length ranged from 1 to 88 months for the 15 participants. Two participants expired 6 and 10 months postoperatively. Five participants showed distant metastasis and the remaining 8 participants were disease-free.

Treatment details: Three participants received neoadjuvant therapy before surgery, and all 15 participants underwent postoperative chemotherapy and radiotherapy including 4 participants receiving targeted therapy and 1 participant receiving immunotherapy.

Pathologic characteristics

Most of the 15 participants had moderately differentiated to well-differentiated glands that were randomly distributed between the fibromuscular walls and infiltrated the cervical canal wall (**Figure 2A**). The glands were partly round, oval, or angular, multi-branched, and folded into the cavity to appear papillary (**Figure 2B**). Some of them were also lobular, micropapillary, and solid, and some were endometrioid. Necrosis and abscesses were seen in the gland cavity (**Figure 2C**). The figure also showed interstitial fibrosis and sclerosis, some interstitial edema, and inflammatory cell infiltration mainly composed of lymphocytes and neutrophils. Well-differentiated and poorly-differentiated areas were commonly found in conjunction, as seen in ductal adenocarcinoma of the prostate or pancreas. Goblet cells were visible, and the majority of cells were tall and columnar, with nuclei observed at the base and minimal atypia. Certain glands had clear atypia with a high nuclear-cytoplasmic ratio. Mitotic figures and apoptotic bodies were visible, but they were less common in G-EAC than in HPV-related adenocarcinoma. Six participants had ovarian metastasis, 9 participants showed vascular invasion, and 6 participants had a maximum tumor diameter greater than or equal to 4 cm.

Table 2. Pathological characteristics of 15 cases of G-EAC

Cases	Gross appearance of cervix	Degree of differentiation	Infiltration depth	Vascular infiltration	Tumor size (cm)
1	ND	Medium-low differentiation	ND	+	ND
2	Erosion	Medium-high differentiation	>2/3	+	4.5×2.0×2.5
3	Erosion	Medium-high differentiation	>2/3	+	4.0×1.5×2.0
4	Erosion	Medium-low differentiation	>2/3	+	2.7×2.5×1.5
5	Erosion	Medium-high differentiation	>2/3	-	3.5×2.0×1.2
6	Erosion, Hard quality	Medium-high differentiation	>2/3	+	5.0×6.0×1.5
7	Erosion	Medium-high differentiation	>2/3	-	ND
8	Erosion	Medium-high differentiation	>2/3	+	5.0×4.0×2.5
9	exogenous	Medium-low differentiation	Middle 1/3 layer	-	1.0×1.0×0.8
10	Erosion	Medium-high differentiation	>2/3	+	3.0×2.0×1.0
11	Erosion	Medium-high differentiation	>2/3	-	3.0×3.0×2.0
12	Erosion	Medium-high differentiation	>2/3	+	4.0×3.0×2.0
13	Erosion	Medium-low differentiation	>2/3	-	4.0×3.8×3.5
14	Erosion	Medium-high differentiation	<1/3	-	2.0×1.2×0.5
15	Erosion	high differentiation	>2/3	-	ND

ND: No done.

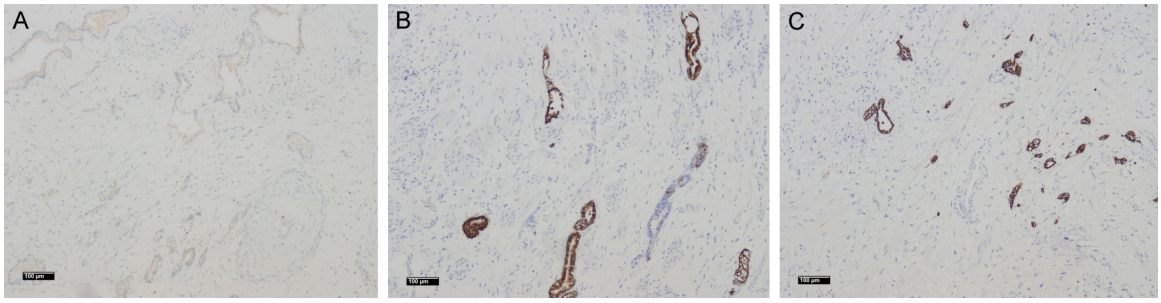

Figure 3. Immunohistochemical staining results of G-EAC for P16, MUC6, and CK7. A: G-EAC were P16 negative (IHC, EnVision, 100×). B: G-EAC were MUC6 positive (IHC, EnVision, 100×). C: G-EAC were CK7 positive (IHC, EnVision, 100×).

Case 2 also showed endometrial glandular mucinous metaplasia (**Figure 2D**). The pathological characteristics of the 15 participants are shown in **Table 2**.

Immunohistochemical characteristics

In total, 18 specimens from the primary and metastatic foci of 15 participants were meaursed tested by immunohistochemical staining, and the positivity rates were as follows: P16 (1/18) (**Figure 3A**), MUC6 (12/14) (**Figure 3B**). MUC5AC (10/11), CK7 (14/14) (**Figure 3C**), CEA (7/11), P53 mutant (11/15), HNF1β (6/6), PAX-8 (7/9), NapsinA (0/5), ER (0/10), PR (0/10), Ki-67 (2%-80%+).

Discussion

Studies have shown that Gastric-type cervical adenocarcinoma (G-EAC) is not associated with high-risk Human papillomavirus (HPV) infection. Gastric-type cervical adenocarcinoma in situ and lobular cervical glandular hyperplasia (LEGH) are precancerous lesions of G-EAC, and they share common molecular genetic alterations, such as the gain of 3q and the deletion of 1p [6]. The gastric-type differentiation expression can be detected in LEGH [7, 8]. The symptoms of G-EAC are not specific compared to cervical HPV-related usual-type adenocarcinoma. The average age of patients in this group was 45.13 years. Ten patients were 30 to 45

years of age. Three participants reported pelvic masses as the initial symptom, hence, they were already in an advanced stage at the time of diagnosis. G-EAC lesions frequently proliferate in the cervical canal, making biopsy-based diagnosis challenging. This study demonstrated a cervical biopsy confirmation rate of 66.67% (10/15). This may be attributable to the following factors: our hospital is a specialized oncology center; and some patients sought consultation with specialist pathologists at a tertiary care institution's pathology department. Imaging plays a critical role in the early diagnosis of G-EAC, with MRI revealing distinct features such as a multilocular and solid-enhanced appearance. The "cosmic pattern" in MRI is strongly indicative of cervical cancer [9, 10]. In this cohort study, 8 participants were diagnosed with cervical cancer based on MRI or PET-CT imaging. Based on our results, 66.67% (6/9) of the participants showed abnormally elevated CA199 levels, indicating that increased CA199 may play a major role in the diagnosis of G-EAC, which is consistent with the findings of Qian [11]. This finding suggests a potential correlation between elevated CA199 levels and the diagnosis of G-EAC, as indicated by both studies.

The term "cervical gastric adenocarcinoma" was proposed by Kojima et al. They described it as a mucinous adenocarcinoma with clear or mildly acidic cytoplasm, well-defined cell boundaries, and rich cytoplasm [3]. It is noteworthy that invasive glandular structures in cervical gastric adenocarcinoma can exhibit a wide range of sizes and shapes, including small cystic glands, crowded tubular glands, and cystic dilated ducts resembling Nabothian cysts. Additionally, complex papillary structures may be observed in cystic areas, with deep invasion into the cervical canal wall [4]. This study also revealed that the presence of inflammatory cells, particularly neutrophils, and eosinophils, along with microabscesses in the gland cavity, is a notable microscopic characteristic of G-EAC. This specific characteristic was observed in 13 participants in this study, shedding light on the potential role of inflammatory response in the pathogenesis of this condition.

MUC5AC, MUC6, and HIK1083 are the primary immunohistochemical markers of G-EAC [1, 12]. MUC5AC expression was rarely positive in G-EAC in this study but frequently positive in normal cervical glands and benign cervical gland lesions (10/11). HIK1083 has not been commercially produced for diagnostic purposes, and immunohistochemical testing for HIK-1083 was not performed for all patients in this study. P16 expression in G-EAC is generally negative or weakly positive with a focal pattern. In this study, immunohistochemical staining for P16 was conducted on 18 specimens, and only case 13 exhibited diffuse and strong positive staining. In situ hybridization of HPV for this case was negative, suggesting that P16 may be diffusely expressed in patients with G-EAC but without HR-HPV infection [13]. Stolnicu and Shanshan Lu found that the mutation rates of P53 in G-EAC were 41% and 57.1%, respectively [14, 15]. In this study, the mutation rate of P53 was slightly higher (73.33%, 11/15). The authors speculated that a mutation of P53 plays a major role in the malignant transformation of G-EAC. CA125 and CK20 were positive in some cases, and ER and PR were commonly negative [16, 17]. This confirmed these findings.

Garg et al. studied the molecular characteristics of G-EAC through next-generation sequencing technology and found that the molecular characteristics of G-EAC were as diverse as their morphology. They detected 92 mutations in 14 samples, with TP53 being the most frequently mutated gene, followed by MSH6, CDKNA/B, POLE, SLX4, ARID1A, STK11, BRCA2, and MSH2 [18]. These abnormalities are mainly associated with DNA damage and repair, cell cycle, Fanconi anemia pathway, and the PI3K/AKT signaling pathway. Many studies have discovered the presence of genetic mutations in STK11/LKB1 in G-EAC spectrum lesions. Additionally, nearly half of patients with PJS have germline mutations in this gene, which are associated with a poor prognosis [19, 20]. Some studies have suggested that the amplification of the human epidermal growth factor receptor-2 (Her-2) is linked to the poor prognosis of patients with G-EAC. Therefore, Her-2 may be a target for the future treatment of G-EAC [21, 22].

It is possible to distinguish well-differentiated G-EAC from the most benign glandular hyperplastic lesions because it usually shows deep infiltration and lacks ER or PR expression. P53 staining displays wild-type features in lobular

cervical glandular hyperplasia, whereas half of well-differentiated G-EAC exhibit mutant results. HPV-associated cervical adenocarcinoma is commonly associated with high-risk HPV infection and is characterized by more pronounced nuclear atypia, increased mitotic figures, and the absence of gastric-type differentiation. Immunohistochemical markers such as P16, HIK1083, MUC6, and MUC5AC, and RNAscope technologies can help differentiate between them. Endometrioid adenocarcinoma can easily be mistaken for G-EAC if it affects the cervix, particularly during segmented curettage biopsy. In this case, immunohistochemistry makes differentiation easier. Most endometrioid carcinomas are positive for ER and PR, while G-EACs are negative for ER and PR. In addition, endometrioid carcinomas and G-EACs are both negative for P16.

A greater challenge is the lack of an established standard treatment method for G-EAC. There is a need for individualized treatments based on established cervical cancer treatment protocols. Due to the possibility of undetectable ovarian metastasis, patients with early-stage cancer are recommended to undergo extensive hysterectomy, bilateral adnexal and pelvic lymph node dissection, para-aortic lymph node dissection, omentectomy and appendectomy. Radiotherapy plus chemotherapy can enhance the efficacy of surgery [2]. Chemotherapy and radiotherapy are administered for patients with advanced-stage cancer. Patients with pelvic masses undergo mass resection, followed by postoperative radiotherapy, chemotherapy, and targeted therapy.

Prognostic factors for G-EAC include tumor diameter equal to or greater than 40 mm, parametrial invasion, lymph node metastasis, poor differentiation, and ovarian metastasis [23]. Case 6 in this study was a specific case because she was 43 years old at the time of surgery, had right ovarian metastases with FIGO stage 4A, and remained 88 months free of recurrence postoperatively. This finding suggests that in certain cases with G-EAC there is a possibility of indolent disease progression, which necessitates more studies.

The prognosis of G-EAC is poorer compared to HPV-associated endocervical adenocarcinoma. Among the 15 patients included in this study, 2 died after survival periods of 6 months and 10 months, respectively, and 5 patients exhibited distant metastasis. Lu et al. reported that one patient developed distant metastasis 6 months after surgery, and the survival lengths of the four patients in their study were 2, 10, 20, and 24 months [15].

In conclusion, this study described the diagnosis and management of 15 patients with G-EAC, summarizing their histopathologic and immunohistochemical features. We found that G-EAC predominantly affects middle-aged individuals, with a higher incidence in advanced stages. Microscopically, the morphology was diverse, but frequently accompanied by intraluminal abscesses and neutrophilic infiltration. Biopsy-based confirmation of G-EAC can be conducted by a specialist pathologist. Overall, the prognosis of G-EAC remains poor, although some patients exhibit slow progression. This study had several limitations, including the lack of HPV testing for three participants, insufficient immunohistochemical analysis in some patients, and the absence of preoperative tumor marker data for several patients.

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Disclosure of conflict of interest

None.

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