Villoglandular adenocarcinoma of cervix: pathologic features, clinical management, and outcome

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Background: The objective of the study was to investigate the management and prognosis of patients with villoglandular adenocarcinoma (VGA) of the uterine cervix.

Materials and methods: The clinical presentation, pathology, management, and prognosis of 41 patients with VGA or other types of cervical adenocarcinoma (ADC) were retrospectively reviewed.

Results: During the patient follow-up period, the proportion of VGA was 8.1% in the cervical ADC cohort (41/507). The median age of the patients with VGA was 41.0 years. The most common presenting symptom was cervical contactive bleeding. There were 38 patients classified as FIGO stage IA1–IB. The median follow-up period was 38.5 months. There were no patient deaths, and only one patient showed recurrence. One of the patients delivered a healthy baby at 34 weeks of gestation prior to treatment with radical hysterectomy. The HPV HC2 test results showed that most patients were positive for HPV infection. HPV 16, 18, and 56 were positive in the 8 patients with HPV type test results. There were significant differences in the grade, depth of stromal invasion, lymph node metastasis, and recurrence between the VGA cases of FIGO stage I and the other types of cervical ADC of FIGO stage I (p<0.05).

Conclusion: This study confirmed that VGA is a type of well-differentiated cervical cancer characterized by shallow stromal invasion, less lymph node metastasis. VGA is associated with less recurrence than other types of cervical ADC.

Keywords: villoglandular adenocarcinoma, uterine cervix, management, prognosis

Introduction
The incidence of cervical adenocarcinoma (ADC) has increased over the past several decades in young women, and there has been a marked decrease in cervical squamous cell carcinoma (SCC).1,2 The proportion of ADC steadily increased from 5% to more than 20%.3 ADC is more difficult to detect and has a worse outcome than SCC. Additionally, ADC has a higher incidence of lymph node metastasis, distant metastases, recurrences, and worse survival outcome.3–5

Villoglandular adenocarcinoma (VGA) of the cervix was first reported by Young and Scully in 1989.6 VGA is a rare well-differentiated subtype of ADC that usually occurs in young women and is associated with a better prognosis than ADC.7,8 Histologically, VGA is a superficially infiltrative tumor with an exophytic growth with long and slender papillary form, limited mitosis, minimal cytologic atypia, and minimal vascular space invasion.9,10 VGA is characterized as superficially infiltrative and shows infrequent lymph node invasion and lymphovascular space invasion.11,12 Therefore,
conservative surgery such as cone biopsy is conducted. However, the present recognition and evaluation of this rare tumor type is limited. In this study, we reviewed the clinical and pathological features of 41 patients with VGA and investigated the risk factors for clinical treatment and prognosis.

**Materials and methods**

The data of patients with ADC from January 1995 to January 2017 (Peking Union Medical College Hospital [PUMCH], People’s Republic of China) were retrospectively reviewed, and written informed consent was obtained from each patient. The procedures were approved by the Ethics Committee of Human Experimentation of PUMCH and are in accordance with the Helsinki Declaration of 1964.

In this study, 41 patients with VGA were identified in the cohort of 507 ADC patients. The standards of pathological VGA diagnosis were the following: 1) a diagnosis made based on complete excision of the primary tumor, rather than on biopsy; 2) the tumor presented as a villoglandular structure or papillary structure with vascular axis, and the invasion is limited to the tumor edge without deep infiltration; and 3) the cellular morphology is relatively mild, nuclei show mild or moderate atypia, and karyokinesis is infrequent. In PUMCH, every pathological diagnosis was made by two pathologists and reviewed by a senior pathologist. Every intractable case would be discussed in department to make sure that the histopathological diagnoses were reliable.

The $\chi^2$ test was used for comparisons of qualitative data and for the clinicopathological parameters between VGA and other types of ADC. Fisher’s exact test was used when the 2 cells (50%) had an expected count less than 5. A t-test was used for the quantitative data. Statistical significance was assumed as $p<0.05$. The statistical analyses were performed using the SPSS 13.0 statistical software.

**Results**

There were 41 patients diagnosed with VGA (8.1%) during the study period. The median patient age was 41.0 years (range, 27–66 years). The most common presenting symptom was cervical contactive bleeding (28/41). The FIGO stage was IA in 4 patients, IB in 34 patients, IIA in 1 patient, and IIB in 2 patients. There were 32 patients who received imaging examinations including color Doppler ultrasonography, magnetic resonance imaging (MRI), computed tomography (CT), and positron emission tomography–computed tomography (PET-CT). The imaging examinations of 28 patients showed cervical placeholder and malignant lesions.

In the cohort of 37 patients who were treated with radical hysterectomy with or without pelvic lymphadenectomy (6/37), 30 patients received bilateral salpingo-oophorectomy (BSO) and 7 received bilateral salpingectomy for ovary conservation. Two patients who desired to preserve fertility received pelvic lymphadenectomy to confirm that there was no lymph node metastasis before receiving further radical vaginal trachelectomy. There were 15 patients who received adjuvant treatments. The detailed treatment descriptions and decisions for treatment are shown in Table 1.

The median follow-up period was 38.5 months (range 19–121 months), and there were no patient deaths during this time. One patient showed recurrent disease. The presenting symptom of the recurrent patient was cervical contactive bleeding, and the cytological test was negative. Additionally, the CA125 level was elevated (69.1 U/mL). The patient was FIGO stage IB1 and underwent nerve-sparing laparoscopic radical hysterectomy, BSO, and pelvic lymphadenectomy. The pathology showed well-differentiated VGA, and the infiltration depth was 5 mm. There were no adjuvant treatments conducted. The tumor recurred in the pelvic 8 months after initial surgery. The PET-CT indicated there was a highly metabolic lesion on the left side of the pelvic floor, and the serum CA125 level was increased to 71.2 U/mL. Exploratory laparotomy was conducted to remove the pelvic mass. The pathology results indicated metastatic ADC. The immunohistochemistry indicated AE1/AE3 (+), CEA (+), p16 (+), and p53 (+). The patient received 6 courses of postoperative chemotherapy. However, at 20 months after the initial surgery, an ultrasound test showed a mass with low density in the vaginal stump. The biopsy results showed well-differentiated VGA. The patient received concurrent chemoradiation therapy.

One patient was diagnosed with VGA at 13 weeks of gestation with FIGO stage IB1. MRI indicated no signs of lymph node metastasis. The patient received conization and cervical cerclage at 16 weeks of gestation. The pathology showed moderately differentiated VGA and there was a negative margin. The patient received 4 courses of chemotherapy with regimens of paclitaxel (240 mg) plus carboplatin (400 mg) at 20 weeks of gestation. At 34 weeks of gestation, the patient underwent cesarean section, radical abdominal hysterectomy, bilateral salpingectomy, and pelvic lymph node dissection. The postoperative pathology was negative. There was no recurrence during the follow-up period of 37 months, and the baby was healthy.

There were 28 patients who received cytological testing within 3 months prior to surgery. There was 1 patient with atypical squamous cells of undetermined significance, and 3 patients showed cervical ADC. Additionally, there were 5 patients with high-grade squamous intraepithelial lesion.
### Table 1: The clinical characteristics, treatment, and follow-up of patients with Vga

| No | Age (years) | Chief complaint | FIGO stage | Treatment | Adjuvant treatment | Follow-up (months) | Recurrence | Outcome |
|----|-------------|-----------------|------------|-----------|--------------------|--------------------|------------|---------|
| 1  | 36          | Diagnosed during regular clinical examination | IA1        | Conization; LRH + BS + ovarian suspension | —                  | 11                 | NED        |
| 2  | 47          | Diagnosed during regular clinical examination | IA1        | Conization; LRH + BSO | —                  | 23                 | NED        |
| 3  | 56          | Cervical contactive bleeding                  | IB1        | RAH + BS + PLND | —                  | 47                 | NED        |
| 4  | 52          | Abnormal vaginal bleeding                     | II B       | RAH + BSO + high ligation of ovarian vein  | NAC + RT + PC      | 88                 | NED        |
| 5  | 58          | Postmenopausal bleeding                       | IA1        | LRH + BSO + PLND | —                  | 31                 | NED        |
| 6  | 33          | Cervical contactive bleeding                  | IB1        | LRH + BSO + PLND | Po-CCRT            | 18                 | NED        |
| 7  | 35          | Diagnosed during regular clinical examination | IB1        | PLND + RVT | —                  | 19                 | NED        |
| 8  | 46          | Abnormal vaginal bleeding                     | IB1        | RAH + BSO + PLND | —                  | 23                 | NED        |
| 9  | 42          | Abnormal vaginal discharge                    | IB2        | RAH + BSO + PLND | NAC + RT + PC      | 32                 | NED        |
| 10 | 50          | Diagnosed during regular clinical examination | IB1        | RAH + BSO + PLND | —                  | 32                 | NED        |
| 11 | 35          | Cervical contactive bleeding                  | IB1        | LRH + BS + PLND | —                  | 25                 | NED        |
| 12 | 41          | Cervical contactive bleeding                  | IB1        | NSLRH + BSO + PLND | —                  | 37                 | + AWD      |
| 13 | 35          | Cervical contactive bleeding                  | IB1        | LRH + BS + PLND | —                  | 26                 | NED        |
| 14 | 46          | Cervical contactive bleeding                  | IB1        | RAH + BSO + PLND | —                  | 29                 | NED        |
| 15 | 66          | Postmenopausal bleeding                       | IB1        | RAH + BSO + PLND | —                  | 104                | NED        |
| 16 | 43          | Diagnosed during regular clinical examination | IB1        | Conization; RAH + BSO + PLND | —                  | 37                 | NED        |
| 17 | 51          | Cervical contactive bleeding                  | IB1        | NSLRH + BSO + PLND | —                  | 18                 | NED        |
| 18 | 47          | Diagnosed during regular clinical examination | IB1        | Conization; RAH + BSO | Pre-CCRT           | 37                 | NED        |
| 19 | 34          | Cervical contactive bleeding                  | IB1        | RAH + BSO + PLND | PC                 | 35                 | NED        |
| 20 | 32          | Cervical contactive bleeding                  | IB2        | NSLRH + BSO + PLND | NAC + Po-CCRT + PC | 32                 | NED        |
| 21 | 32          | Abnormal vaginal discharge                    | IB1        | LRH + BSO + PLND | —                  | 12                 | NED        |
| 22 | 36          | Abnormal vaginal discharge                    | IB1        | Conization + UCC, CS + RAH + BS + PLND  | NAC                 | 20                 | NED        |
| 23 | 32          | Cervical contactive bleeding                  | IB1        | LRH + BS + PLND | —                  | 12                 | NED        |
| 24 | 55          | Cervical contactive bleeding                  | IB1        | NSLRH + BSO + PLND + PALND | Po-CCRT           | 6                  | NED        |
| 25 | 38          | Cervical contactive bleeding                  | IB1        | NSLRH + BSO + PLND + PALND | Po-CCRT           | 23                 | NED        |
| 26 | 27          | Abnormal vaginal discharge                    | IB1        | PLND + RVT | PC                 | 4                  | NED        |
| 27 | 44          | Cervical contactive bleeding                  | IB1        | LRH + BSO + PLND | —                  | 12                 | NED        |
| 28 | 40          | Abnormal vaginal discharge                    | IB1        | LRH + BS + PLND | —                  | 14                 | NED        |
| 29 | 49          | Abnormal vaginal discharge                    | IB1        | RAH + BSO + high ligation of ovarian vein + PLND | Po-CCRT           | 20                 | NED        |
| 30 | 41          | Cervical contactive bleeding                  | IB1        | LRH + BSO + PLND | —                  | 6                  | NED        |
| 31 | 40          | Cervical contactive bleeding                  | IB1        | LRH + BSO + PLND | —                  | 5                  | NED        |
| 32 | 41          | Diagnosed during regular clinical examination | IB1        | RAH + BSO + PLND | NAC + Pre-CCRT     | 2                  | NED        |
| 33 | 30          | Cervical contactive bleeding                  | IB1        | Conization; NSARH + BS + PLND + PALND + ovarian suspension | Po-CCRT           | 49                 | NED        |
| 34 | 34          | Cervical contactive bleeding                  | IB2        | Conization; RAH + BSO + PLND | NAC + Po-CCRT     | 49                 | NED        |
| 35 | 45          | Cervical contactive bleeding                  | IB1        | RAH + BSO + PLND | —                  | 16                 | NED        |
| 36 | 45          | Cervical contactive bleeding                  | IB1        | RAH + BSO + PLND | —                  | 10                 | NED        |
| 37 | 60          | Cervical contactive bleeding                  | IB1        | LRH + BSO + PLND + PALND | —                  | 11                 | NED        |
| 38 | 64          | Cervical contactive bleeding                  | IB2        | LRH + BSO | Pre-CCRT          | 11                 | NED        |
| 39 | 28          | Cervical contactive bleeding                  | IB1        | Conization | —                  | 5                  | NED        |
| 40 | 32          | Diagnosed during regular clinical examination | IB1        | Conization | —                  | 10                 | NED        |
| 41 | 46          | Cervical contactive bleeding                  | IB1        | RAH + BSO + PLND | —                  | 59                 | NED        |

**Abbreviations:** Vga, villoglandular adenocarcinoma; AWD, alive with disease; BS, bilateral salpingectomy; BSO, bilateral salpingo-oophorectomy; Po-CCRT, postoperative concurrent chemoradiation therapy; Pre-CCRT, preoperative concurrent chemoradiation therapy; CS, cesarean section; LRH, laparoscopic radical hysterectomy; NAC, neoadjuvant chemotherapy; NED, no evidence of disease; NSARH, nerve-sparing abdominal radical hysterectomy; NSLRH, nerve-sparing laparoscopic radical hysterectomy; PC, postoperative chemotherapy; PALND, paraaortic lymph node dissection; PLND, pelvic lymph node dissection; RAH, radical abdominal hysterectomy; RT, radiation therapy; RVT, radical vaginal trachelectomy; UCC, uterine cervical cerclage.
and 6 patients with atypical glandular cell. The remaining 13 patients had negative results. We found that 9 of 12 patients with HPV HC2 test results were positive for HPV infection. HPV 16, 18, and 56 were positive in the 8 patients with HPV type test results. The cytology and HPV testing results are shown in Table 2. The immunohistochemistry results indicated positive p16 and Ki-67 expression but negative PR and ER expression in most patients.

There were 41 patients with VGA and 326 patients with ADC who received radical hysterectomy in the cohort of 507 ADC patients. The clinicopathological parameters of the 41 patients with VGA and 326 patients with ADC were compared. The data in Table 3 show that there were significant differences in the grade, depth of stromal invasion, lymph node metastasis, and recurrence between the VGA cases of FIGO stage I and the other types of cervical ADC of FIGO stage I (p<0.05). VGA is a type of well-differentiated cervical cancer characterized by shallow stromal invasion, less lymph node metastasis, and less recurrence than other types of cervical ADC.

### Discussion

VGA of the cervix has a younger patient prevalence and better prognosis than other variants of cervical ADC. As shown in Table 4, we reviewed the VGA literature for the cervix and found there was a total of 203 patients with VGA reported. The patients’ ages ranged from 33 to 52 years, and the majority of patients were FIGO stage I. There were 15 patients presenting with LVI, 7 patients with LN metastasis, 12 patients with recurrence, and 8 patients who died of this disease.6,7,12,13,15–24

In this study, 1 patient had disease recurrence and was alive with disease. There were no obvious risk factors in this patient except for the consistent elevated serum CA125 level during the preoperative and follow-up period.

The favorable prognosis for VGA patients permits a more conservative surgical approach in selected patients including

### Table 2: Cytological test and HPV test with VGA of the cervix

| Patient | Cytological test | HPV type test | HC2 HPV DNA | Clinical symptoms | Outcome |
|---------|------------------|---------------|-------------|-------------------|---------|
| 1       | AGC              | HPV 18+, HPV 56+ |             | Diagnosed during regular clinical examination | NED     |
| 3       | N                | 0.7           |             | Cervical contactive bleeding | NED     |
| 5       | ADC              | Postmenopausal bleeding | |             | NED     |
| 6       | N                | 16.79         |             | Cervical contactive bleeding | NED     |
| 7       | HSIL             | 37.16         |             | Diagnosed during regular clinical examination | NED     |
| 8       | AGC              | Abnormal vaginal bleeding | |             | NED     |
| 10      | N                | Diagnosed during regular clinical examination | |             | NED     |
| 11      | ASCUS            | 1768.5        |             | Cervical contactive bleeding | NED     |
| 12      | N                | Cervical contactive bleeding | |             | AWD     |
| 13      | N                | Cervical contactive bleeding | |             | NED     |
| 15      | AGC              | Postmenopausal bleeding | |             | NED     |
| 16      | AGC              | Diagnosed during regular clinical examination | |             | NED     |
| 18      | HSIL             | HPV 18+       | 287.1       | Diagnosed during regular clinical examination | NED     |
| 19      | HSIL             | Cervical contactive bleeding | |             | NED     |
| 21      | ADC              | 84.62         | Abnormal vaginal discharge | NED     |
| 22      | N                | Abnormal vaginal discharge | |             | NED     |
| 23      | N                | HPV 16+       | 114         | Abnormal vaginal discharge | NED     |
| 27      | HSIL             | Cervical contactive bleeding | |             | NED     |
| 28      | N                | 5.64          | Abnormal vaginal discharge | NED     |
| 29      | N                | Abnormal vaginal discharge | |             | NED     |
| 30      | N                | HPV 16+       | 1402.69     | Diagnosed during regular clinical examination | NED     |
| 33      | N                | 6.87          | Abnormal vaginal discharge | NED     |
| 35      | AGC              | Cervical contactive bleeding | |             | NED     |
| 36      | ADC              | HPV 16+, HPV 18+ | |             | NED     |
| 37      | N                | Cervical contactive bleeding | |             | NED     |
| 38      | N                | HPV 16+       | 6.87        | Cervical contactive bleeding | NED     |
| 39      | N                | HPV 16+, HPV 18+ | |             | NED     |
| 40      | N                | Cervical contactive bleeding | |             | NED     |
| 41      | N                | Cervical contactive bleeding | |             | NED     |

**Abbreviations:** VGA, villoglandular adenocarcinoma; ADC, adenocarcinoma; AGC, atypical glandular cell; AWD, alive with disease; ASCUS, atypical squamous cells of undetermined significance; HSIL, high-grade squamous intraepithelial lesion; N, negative; NED, no evidence of disease.
young women with localized disease and those who wish to maintain fertility.25 There were 16 patients reported in the literature who underwent fertility-preserving surgery such as cervical conization and radical trachelectomy.6,7,12,13,15–24 In this study, 2 patients who desired to preserve fertility received pelvic lymphadenectomy to rule out lymph node metastasis. Radical vaginal trachelectomy was then conducted, and there was no recurrence during the follow-up period. Currently, surgical resection range and treatment options for ADC patients are considered to be uses in VGA patients. But, our clinical data and previous studies indicate that VGA is less invasive than ADCs. As VGA has more positive prognosis, the surgery extent could be narrowed for stage I VGA patients. This is what should be further studied in future.

The treatment for cervical cancer associated with pregnancy is complicated, and there is currently no specific treatment scheme. Previous studies reported less radical fertility-sparing surgery for patients in FIGO stage IA2–IB1. The treatment included laparoscopic pelvic lymphadenectomy and cervical conization, which was then followed by neoadjuvant chemotherapy.26–28 In the VGA patients of this study, we compared the recurrence between with and without adjuvant treatment; the patients with adjuvant treatment showed less recurrence rate (p<0.001). Several studies compared primary surgery or concurrent chemoradiation therapy in pregnant women with FIGO stage IB cervical cancer with delivery delay. Neoadjuvant chemotherapy of paclitaxel plus cisplatin followed by radical surgery and postoperative chemotherapy could be considered a feasible alternative to preserve fertility.29,30 One patient in this study maintained pregnancy until 34 weeks of gestation before radical hysterectomy and delivered a healthy baby. MRI for this patient indicated no lymph node metastasis, and cervical conization confirmed the pathological type, grade, depth of stromal invasion, and lymph vascular space invasion. The patient was treated using neoadjuvant chemotherapy with paclitaxel plus cisplatin during the second trimester.

VGA is a rare tumor type that accounts for approximately 5% in cervical ADCs.17 This tumor is histologically characterized by tall and thin papillae with minimal cellular atypia. The characteristic histological features of various epithelia have been reported, and it is known that the papillae are lined by 1 or more layers of cells with endocervical, endometrioid, or intestinal differentiation.31 In this study, preoperative cytological tests were negative in 11 patients (28.9%). The results from the study by Choi et al indicate the abnormal architectural patterns such as three-dimensional papillary structures, nuclear overlapping, and nuclear hyperchromasia are important clues to suspect the possibility of a VGA. However, liquid-based cytology shows better preserved nuclear details such as prominent nucleoli and irregular nuclear membranes and can facilitate the diagnosis of VGA.23

Table 3 Comparison of VGA with other ADCs of FIGO I on clinicopathological parameters

| Characteristics                  | VGA (n=38) | ADC (n=226) | p    |
|----------------------------------|------------|-------------|------|
| Age (median, range), years       | 41 (26–66) | 42 (20–72)  | 0.42 |
| FIGO stage                       |            |             | 0.44 |
| IA                               | 4          | 31          |      |
| IB1                              | 31         | 151         |      |
| IB2                              | 3          | 44          |      |
| Grade                            |            |             | 0.000|
| Well                             | 33         | 109         |      |
| Moderate                         | 5          | 70          |      |
| Poor                             | 0          | 45          |      |
| Tumor size (≤4 cm)               | 35         | 189         | 0.158|
| (>4 cm)                          | 3          | 35          |      |
| Depth of stromal invasion        |            |             | 0.000|
| ≤1/2                             | 36         | 145         |      |
| >1/2                             | 2          | 81          |      |
| LVSI                             |            |             | 0.060|
| Negative                         | 37         | 194         |      |
| Positive                         | 1          | 32          |      |
| Vaginal resection margin         |            |             | 0.433|
| Negative                         | 35         | 215         |      |
| Positive                         | 3          | 11          |      |
| Parametrial invasion             |            |             | 0.324|
| Negative                         | 36         | 220         |      |
| Positive                         | 2          | 6           |      |
| LN metastasis                    |            |             | 0.001|
| Negative                         | 37         | 194         |      |
| Positive                         | 1          | 32          |      |
| Ovary preservation               |            |             | 0.239|
| No                               | 29         | 191         |      |
| Yes                              | 9          | 35          |      |
| Recurrence                       |            |             | 0.038|
| No                               | 37         | 193         |      |
| Yes                              | 1          | 33          |      |

Abbreviations: VGA, villoglandular adenocarcinoma; ADCs, adenocarcinomas; LN, lymph node; LVSI, lymph vascular space invasion.
further investigated. Second, the sample population is limited for this rare tumor, and it is difficult to distinguish VGA from other types of ADC. Thus, it is critical to perform a meta-analysis or more multicenter prospective studies to investigate the most accurate diagnosis and proper treatment for VGA.

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Disclosure
The authors report no conflicts of interest in this work.

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Table 4 Literature review of VGA

| Reference                  | Cases | Age | Stage | SI | LVI | LN metastasis | Fertility preserving | Recurrence | DOD |
|----------------------------|-------|-----|-------|----|-----|---------------|----------------------|------------|-----|
| Young and Scully4          | 13    | 33  | I13   |    |     |               |                      |            |     |
| Kaku et al15               | 7     | 45  | I10   |    |     |               |                      |            |     |
| Utsugi et al16             | 13    | 45  | I10   |    |     |               |                      |            |     |
| Khunamornpong et al17      | 15    | 39  | I14   |    |     |               |                      |            |     |
| Jones et al7               | 24    | 37  | ND    |    |     |               |                      |            |     |
| Costa et al12              | 4     | 52  | ND    |    |     |               |                      |            |     |
| Lataifeh et al18           | 28    | 38  | I19   |    |     |               |                      |            |     |
| Kim et al19                | 15    | 40  | ND    |    |     |               |                      |            |     |
| Jones et al20              | 12    | 38  | ND    |    |     |               |                      |            |     |
| Hopson et al13             | 3     | 35  | I3    |    |     |               |                      |            |     |
| Reed et al11               | 5     | 34.2| ND    |    |     |               |                      |            |     |
| Korach et al21             | 9     | 38.8| I8    |    |     |               |                      |            |     |
| Choi et al22               | 3     | 47  | ND    |    |     |               |                      |            |     |
| Hagiwara et al24           | 8     | 36  | I7    |    |     |               |                      |            |     |
| Stanley-Christian et al8   | 3     | 33  | I3    |    |     |               |                      |            |     |
| Present study              | 41    | 42  | I38   |    |     |               |                      |            |     |

Abbreviations: VGA, villoglandular adenocarcinoma; DOD, died of disease; LN, lymph node; LVI, lymph vascular space invasion; ND, not described; SI, stromal invasion.
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