Adenocarcinoma of the cervix: Its prognosis and difficult pathological diagnosis

（子宮頸部腺癌の予後の検討と組織診断の困難さ）

申 請 者　　弘前大学大学院医学研究科

腫瘍制御科学領域　婦人科腫瘍学教育研究分野

氏　　名　　追切　裕江

指導教授　　横山　良仁

Adenocarcinoma of the cervix: Its prognosis and difficult pathological diagnosis

H. Oikiri1, M. Futagami1, J. Watanabe2, Y. Yokoyama1*
1 Department of Obstetrics and Gynecology, Hirosaki University School of Medicine, 5-Zaifu-cho, Hirosaki, 036-8562, Japan
2 Department of Cellular and Hist-Pathology, Division of Medical Life Science, Hirosaki University Graduate School of Health Science, Hirosaki, Aomori 036-8564, Japan
*Corresponding author:
Yoshihito Yokoyama, M.D.,
Department of Obstetrics and Gynecology, Hirosaki University School of Medicine, 5-Zaifu-cho, Hirosaki, Aomori, 036-8562, Japan.
Email: yokoyama@cc.hirosaki-u.ac.jp
Tel: +81-172-39-5107 Fax: +81-172-37-6842

Summary

Purpose of investigation: Adenocarcinoma (AC) of the cervix is considered to have a worse prognosis than squamous cell carcinoma (SCC). The incidence of AC of the cervix has increased over the past few years. The WHO's classification of AC of the cervix was revised in 2014, and usual-type endocervical AC and gastric-type mucinous AC were added as new classes of AC of the cervix. The current study reassessed AC of the cervix in accordance with the new classification and it examined the prognosis for AC of the cervix.

Subjects and methods: Subjects were 204 patients who were diagnosed with cervical cancer at this Hospital from 2001 to 2011. Age at onset, histology, FIGO's staging classification, treatment, and the 5-year survival rate for these patients were examined retrospectively. The histopathology of cancer previously identified as AC was reassessed in accordance with the 2014 WHO classification of AC of the cervix.

Results: SCC was identified in 165 patients (81%), AC was identified in 22 (11%), adenosquamous carcinoma (ASC) was identified in 9 (4%), and some other form of cancer was identified in 8 (4%). Median age at onset was 52 years for patients with SCC and 44 years for patients with AC/ASC. According to FIGO's staging classification, SCC was stage I in 79 patients (48%) and AC/ASC was stage I in 21 patients (68%), SCC was stage II in 41 patients (25%) and AC/ASC was stage II in 5 patients (16%), SCC was stage III in 28 patients (17%) and AC/ASC was stage III in 1 patient (3%), and SCC was stage IV in 16 patients (10%) and AC/ASC was stage IV in 4 patients (13%). The 5-year survival rate (Kaplan-Meier method) was 89.3% for patients with SCC undergoing initial surgery and 91.7% for patients with AC/ASC undergoing initial surgery. The 5-year survival rate for patients undergoing initial surgery did not differ significantly (log-rank test, p=0.84). The 5-year survival rate was 92%

for patients with stage I-II AC/ASC who underwent surgery and 50% for patients with stage I-II AC/ASC who received radiation therapy (including concurrent chemotherapy and radiation therapy). The 5-year survival rate for patients with stage I-II AC/ASC differed significantly depending on whether the patient underwent surgery or not ($p < 0.02$). Reassessment of AC resulted in a different diagnosis in 8 (38%) of 21 patients with AC. Reassessment in this study resulted in 6 patients who were diagnosed with endometrioid AC all being diagnosed with usual-type endocervical AC instead.

Conclusion: AC/ASC is considered to have a poor prognosis, but the current results suggested that surgery can result in a good prognosis if lesions can be removed. The histopathologic subtype of AC is often determined by a diagnostician, and this determination is difficult.

Key words: Adenocarcinoma of the cervix, usual-type endocervical adenocarcinoma, 5-year survival rate, surgery

Content

Adenocarcinoma (AC) has poor prognosis, but surgery can result in good prognosis. Determination of histopathologic subtype of AC is difficult.

Introduction

In Japan, morbidity and mortality from cervical cancer have increased over the past few years. The most prevalent histology of cervical cancer is squamous cell carcinoma (SCC), followed by adenocarcinoma (AC). Over the past few years, AC has increased particularly among younger women; in developed countries, AC accounts for 20-25% of all cervical cancer and it accounts for 22% of all cervical cancer in Japan (1). Treatment for SCC is typically surgery for early cancer and concurrent chemotherapy and radiation therapy (CCRT) for advanced cancer, but AC and adenosquamous carcinoma (ASC) are resistant to radiation therapy and chemotherapy. This aspect affects residual disease and the patient's prognosis. AC/ASC is considered to have a worse prognosis than SCC (2).

The WHO's classification of tumors of the female reproductive organs was revised in 2014, and the framework for adenocarcinoma (AC) of the cervix was reorganized (3). AC of the cervix is divided into usual type endocervical AC, mucinous AC, villoglandular AC, endometrioid AC, clear cell AC, serous AC, and mesonephric AC, and mucinous AC includes intestinal type mucinous AC, gastric-type mucinous AC, signet-ring cell-type mucinous AC, minimal deviation mucinous AC. The most prevalent form of AC of the cervix is endocervical mucinous AC, and endocervical mucinous AC accounts for about 90% of all AC of the cervix. In fact, however, "mucinous" AC often lacks cytoplasmic mucins, so that form of cancer was renamed usual-type AC, distinguishing it from true mucinous AC (3). In the past, mucinous AC included intestinal AC and signet-ring cell-type AC, but the recent revision to the WHO classification added gastric-type AC as a new histologic subtype and it identified minimal

deviation AC as a specific type of very highly differentiated gastric-type AC (3). In addition, villoglandular carcinoma has been classified as an independent subtype along with usual-type AC, mucinous AC, and serous AC. Usual-type AC and intestinal mucinous AC are often HPV-related tumors, but special forms of AC such as gastric-type AC, clear cell AC, serous AC, and mesonephric AC are negative for HPV or HPV is detected infrequently. Thus, these forms of AC must be viewed as histologic subtypes that can frustrate HPV DNA testing and HPV vaccines. Gastric-type AC in particular is prevalent in Japan, and its treatment will probably be discussed in the future (4).

The current study focused on AC and ASC. This study reassessed AC in accordance with the new classification and it examined the prognosis for AC and ASC.

Subjects and Methods

Subjects were 204 patients who were diagnosed with cervical cancer at Hirosaki University Hospital over an 11-year period from 2001 to 2011. Age at onset, histology, FIGO's staging classification, treatment, and the 5-year survival rate for these patients were examined retrospectively. Of the 204 patients, 8 were diagnosed with a neuroendocrine tumor, malignant lymphoma, carcinosarcoma, or adenoid basaloid AC. Given the small sample sizes, those 8 patients were excluded from this study. The histopathology of cancer that was identified as AC was reassessed by a gynecologist (H.O.) and a pathologist (J.W.) in accordance with the 2014 WHO classification of AC of the cervix.

The OS was calculated using the Kaplan-Meier method. A log-rank test was used to assess statistical significance. Median values between the groups were compared using Mann-Whitney's U test, and $p < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS (version 21, SPSS Inc., Chicago, IL, USA).

Results

Clinical aspects of cervical cancer

In the 204 patients, histology was SCC in 81% (165 / 204), AC in 11% (22/204), ASC in 4% (9/204), and some other form of cancer in 4% (8/204). That other form of cancer was a neuroendocrine tumor in 5 patients, malignant lymphoma in 1, carcinosarcoma in 1, and adenoid basaloid AC in 1. The median age at onset was 52 years (youngest age: 23 years, oldest age: 89 years) for patients with SCC and 44 years (youngest age: 27 years, oldest age: 80 years) for patients with AC/ASC. The median age at onset did not differ significantly (Mann-Whitney's U test, $p=0.94$).

According to FIGO's staging classification, SCC was stage I in 48% of patients (79/165) and AC/ASC was stage I in 68% (21/31), SCC was stage II in 25% (41/165) and AC/ASC was stage II in 16% (5/31), SCC was stage III in 17% (28/165) and AC/ASC was stage III in 3% (1/31), and SCC was stage IV in 10% (16/165) and AC/ASC was stage IV in 13% (4/31). The

stage of SCC was indeterminate in 1 patient. AC was histopathologically reassessed based on the 2014 WHO classification of AC of the cervix. Usual-type endocervical AC was identified in 82% of patients (18/22), gastric-type mucinous AC was identified in 14% (3/22), and AC was unclassifiable in 4% (1/22). Fifty-three percent of patients (87/165) with SCC and 77% of patients (24/31) with AC/ASC underwent initial treatment in the form of surgery. Forty-seven percent of patients (78/165) with SCC and 23% of patients (7/31) with AC/ASC received initial treatment in the form of radiation therapy or CCRT. The 5-year survival rate for patients with SCC and patients with AC/ASC was compared in terms of less advanced cancer (stage I-II) and more advanced cancer (stage III-IV) (Fig. 1). Patients who died from other causes were excluded from this comparison, and only patients who died from cancer were included. The 5-year survival rate was 87.5% for patients with stage I-II SCC and 88.4% for patients with stage I-II AC/ASC (Fig. 1). The 5-year survival rate was 44.1% for patients with stage III-IV SCC and 40% for patients with stage III-IV AC/ASC (Fig. 1). The 5-year survival rate for patients with less advanced SCC or AC/ASC (stage I-II) and patient with more advanced SCC or AC/ASC (stage III-IV) did not differ significantly (log-rank test, $p=0.63$, $p=0.81$). The 5-year survival rate was 89.3% for patients with SCC undergoing initial surgery and 91.7% for patients with AC/ASC undergoing initial surgery. The 5-year survival rate for patients undergoing initial surgery did not differ significantly (log-rank test, $p=0.85$) (Fig. 2A). In other words, patients with stage I-II cancer who underwent initial surgery had a good prognosis, regardless of histology. The 5-year survival rate was 89.3% (n=86) for patients with stage I-II SCC who underwent surgery and 86.8% (n=28) for patients with cancer in the same stage who received radiation therapy (including CCRT) while the 5-year survival rate was 91.7% (n=22) for patients with stage I-II AC/ASC who underwent surgery and 50% (n=4) for patients with cancer in the same stage who received radiation therapy (including CCRT). Patients who underwent surgery had a significantly better prognosis (log-rank test, $p<0.02$) (Fig. 2B).

Histopathologic diagnosis of AC of the cervix

Twenty-one cases of cancer that was previously identified pathologically as AC were reassessed by a gynecologist and a pathologist in accordance with the 2014 WHO classification of AC of the cervix (Table 1). One out of the 22 AC cases was excluded from this evaluation since preservation of the stained slides was poor. During that reassessment, cancer identified as AC was not identified as SCC instead. Reassessment resulted in a different diagnosis in 8 (38%) of 21 patients with AC. Reassessment in this study resulted in 6 patients who were diagnosed with endometrioid AC all being diagnosed with usual-type endocervical AC instead. Results suggested that endometrioid AC is difficult to differentiate from usual-type endocervical AC lacking cytoplasmic mucins (Fig. 3). Diagnoses by the gynecologist and the pathologist differed for patient 1. In patient 1, some tissue indicative of

usual-type endocervical AC and some tissue indicative of gastric-type mucinous AC were both present (Fig. 4A, B). p16 and HIK-1083 immunostaining were performed to make a differential diagnosis; usual-type AC is strongly positive for p16 while gastric-type AC is positive for HIK-1083. The AC component was weakly positive for HIK-1083 and certain areas were positive for p16 (Fig. 4C, D). Definitive results were not obtained. The cancer could not be definitively identified as gastric-type mucinous AC, so a diagnosis of usual-type endocervical AC was considered appropriate.

Discussion

AC of the cervix has increased over the past few years (5). It has increased particularly among younger women, presumably because of increased use of oral contraceptives, increased infection with HPV16 or 18, and first pregnancy at a younger age (6). Recent studies have reported that the histology of cervical cancer is SCC in 75% of cases, AC in 15-25%, and ASC in 2-3% (7, 8). At the current authors' hospital, the histology of cervical cancer is SCC in 81% of cases, AC in 11%, and ASC in 4%, so the percentages are roughly similar. A comparison of the median age at the onset of SCC or AC/ASC indicated that the median age at the onset of SCC was 52 years while the median age at the onset of AC/ASC was 44 years. AC/ASC tended to develop at a younger age. ASC often develops in relatively younger patients (9). In fact, the median age of patients with ASC at the current authors' hospital was 43 years, which is young. In contrast, the median age of patients with AC was 44 years, which is also relatively young. The current results suggested that AC is increasing among younger women seen at this Hospital.

AC is considered to have a worse prognosis than SCC because metastasis occurs early on, detection is delayed, the cancer is resistant to radiation therapy, and the cancer has a particular histology (4). Various studies have examined the prognosis for ASC, but their findings are inconsistent. According to FIGO's Annual Report, the 5-year survival rate for patients with AC or SCC by stage is 65.3% for stage Ib2 AC versus 79.5% for stage Ib2 SCC, 55.9% for stage IIb AC versus 67.4% for stage IIb SCC, and 23.7% for stage IIIb AC versus 44.0% for stage IIIb SCC (10). AC has a worse prognosis. In the current study, however, the prognosis for AC/ASC and SCC did not differ significantly in terms of the 5-year survival rate for patients with less advanced cancer (stage I-II) or more advanced cancer (stage III-IV) and the 5-year survival rate for patients undergoing initial surgery. This suggests that AC/ASC has a relatively good prognosis at this Hospital. There are 2 reasons for this. First, more patients in the current study had stage I-II AC/ASC than had stage I-II SCC (84% for the former versus 73% for the latter). Accordingly, 77% of patients with AC/ASC underwent initial surgery while 53% of patients with SCC underwent initial surgery. Second, more patients with AC/ASC were initially diagnosed and lesions were completely removed through initial surgery. The 5-year survival rate for patients with stage I-II AC by treatment also indicated

that patients undergoing initial surgery had a significantly better prognosis than patients receiving radiation therapy or chemotherapy. Thus, surgery should be chosen to treat stage I-II AC/ASC to the extent possible. AC/ASC is considered to have a poor prognosis, but AC/ASC can presumably have as good a prognosis as SCC if surgery is performed early on and the tumor is removed.

In Japan, cervical cancer is currently diagnosed based on the 2014 WHO classification of AC of the cervix. In the past, endocervical AC was the most prevalent form of "mucinous" AC, but endocervical AC actually lacks cytoplasmic mucins, so it is distinct from mucinous AC. Endocervical AC has been classified separately in the WHO classification as usual-type endocervical AC. Gastric-type mucinous AC in particular has a worse prognosis than other forms of AC of the cervix, and gastric-type mucinous AC has been added to the WHO classification as a new histologic subtype. High-risk HPV is associated with the development of endocervical AC, but it is not associated with the development of gastric-type mucinous AC. Typically, gastric-type mucinous AC is often detected in an advanced stage, and metastases are often found during initial treatment (11). A study comparing the 5-year survival rate for patients with endocervical AC and patients with gastric-type mucinous AC reported that 5-year survival rate was 91% for patients with endocervical AC and 42% for patients with gastric-type mucinous AC (12). Thus, the prognosis for AC differs depending on the histologic subtype, so a diagnosis based on histopathology is crucial.

In the current study, the gynecologist identified endocervical AC in patient 1 while the pathologist identified gastric-type mucinous AC. The 2003 WHO classification of cervical neoplasms classified gastric-type mucinous AC other than minimal deviation adenocarcinoma (MDA) as endocervical mucinous AC. Thus, endocervical AC is difficult to identify. Some tissue had aspects of lobular endocervical glandular hyperplasia (LEGH) along with gastric-type mucinous AC, so the pathologist identified irregular ductal structures adjected to that tissue as gastric-type mucinous AC. However, the cancer was identified as endocervical AC based on the results of HIK-1083 and p16 immunostaining. MDA consists of very well-differentiated gastric-type mucinous AC and it lacks cellular atypia almost entirely, so it is difficult to differentiate from benign endocervical glandular proliferation. Thus, immunostaining tissue for gastric‐type mucins such as HIK-1083 and MUC6 is useful in making a differential diagnosis (13, 14). Over the past few years, kits to sample gastric‐type mucins during cervical cytology have become common. LEGH is a benign disease that produces gastric‐type mucins, so it is difficult to differentiate from MDA. However, LEGH is predominantly located closer to the internal orifice of the uterus than MDA, and MRI often reveals relatively well-defined medium to large cysts. LEGH and MDA can be differentiated in light of these aspects (15). Gastric-type mucinous AC is prevalent in Japan and it has a worse prognosis than other forms of AC, so early diagnosis is crucial (4).

Six of 21 patients who were diagnosed with endometrioid AC were diagnosed with endocervical AC instead. Endocervical AC and endometrioid AC are similar in that both have columnar tumor cells lacking mucins. In endometrioid AC, mucins are completely absent from tumor cells, but ciliated cells are present on the surface of the glandular lumen like in endometrioid AC of the endometrium. In actuality, differentiating endocervical AC and endometrioid AC is difficult, and the determination is heavily influenced by the diagnostician. The same was true in the current patients. Endometrioid AC is said to account for less than 5% of AC of the cervix (16), but the actual prevalence of endometrioid AC varies depending on the study. This presumably reflects the difficulty of differentiating endocervical AC and endometrioid AC.

Conclusion

If the tumor is removed completely through surgery, AC of the cervix is likely to have a good prognosis. Nevertheless, identifying the histologic subtype of AC of the cervix is extremely difficult, and future advances need to be made to properly identify those subtypes.

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Table 1. A gynecologist and a pathologist's reassessment of the histology of cancer previously identified as uterine adenocarcinoma in accordance with the WHO's new classification of adenocarcinoma of the cervix

Case	Age	Stage	Previous identification	Reevaluation by a gynecologist	Reevaluation by a pathologist
1	61	IIa	UEA	UEA	GMA
2	30	Ib2	UEA	UEA	UEA
3	40	Ib1	UEA	UEA	UEA
4	74	IIb	UEA	UEA	UEA
5	43	IVa	UEA	UEA	UEA
6	39	Ib1	UEA	UEA	UEA
7	27	Ib1	UEA	UEA	UEA
8	55	Ib1	UEA	UEA	UEA
9	42	Ib1	UEA	UEA	UEA
10	62	IVa	UEA	UEA	UEA
11	49	Ib1	UEA	UEA	UEA
12	53	Ib2	EC	UEA	UEA
13	53	Ib1	EC	UEA	UEA
14	44	Ib2	EC	UEA	UEA
15	41	Ib1	EC	UEA	UEA
16	37	Ib1	EC	UEA	UEA
17	36	Ib1	EC	UEA	UEA
18	50	Ia	MDA	MDA	MDA
19	54	Ia2	MDA	MDA	MDA
20	58	IVa	Adenocarcinoma, NOS	GMA	GMA
21	59	Ib1	Adenocarcinoma, NOS	Adenocarcinoma, NOS	Adenocarcinoma, NOS

UEA: usual-type endocervical adenocarcinoma (endocervical-type mucinous adenocarcinoma before the WHO classification was revised), GMC: gastric-type mucinous carcinoma of the cervix, EC: endometrioid carcinoma, MDA: minimal deviation adenocarcinoma of the cervix, NOS: not otherwise specified

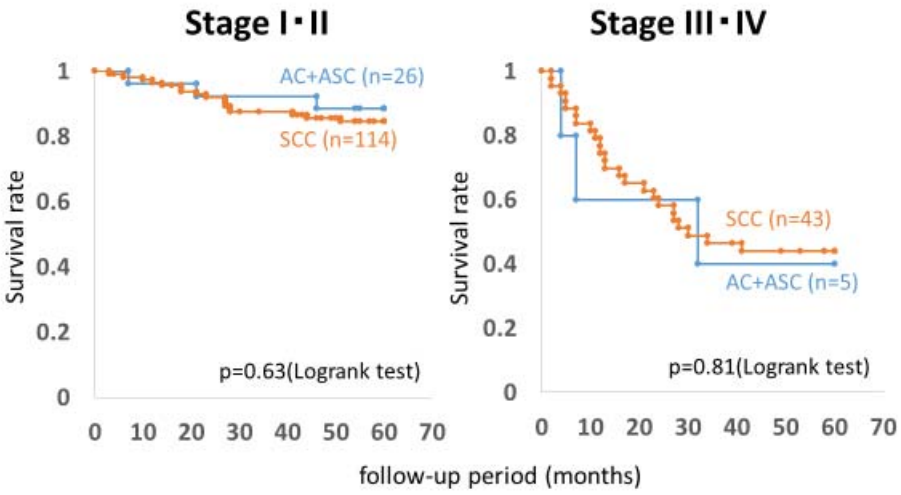

Figure.1

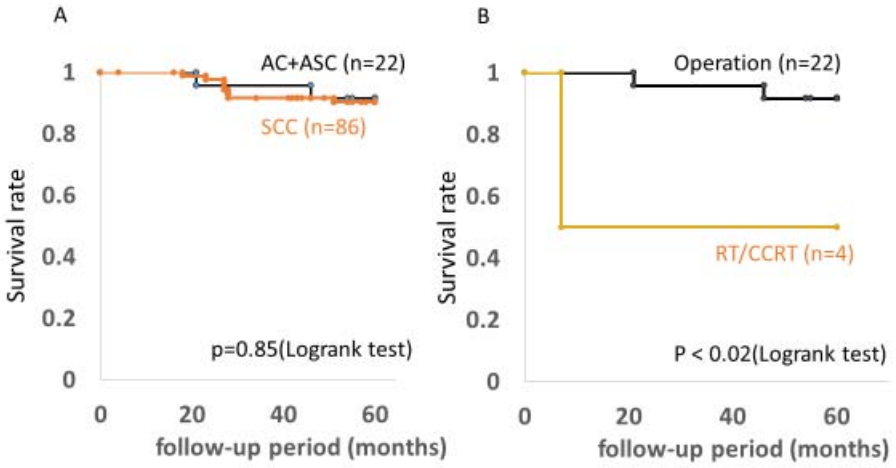

Figure. 2

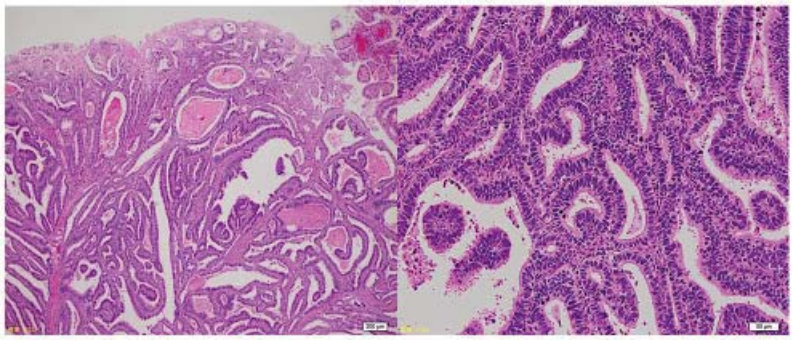

Figure. 4

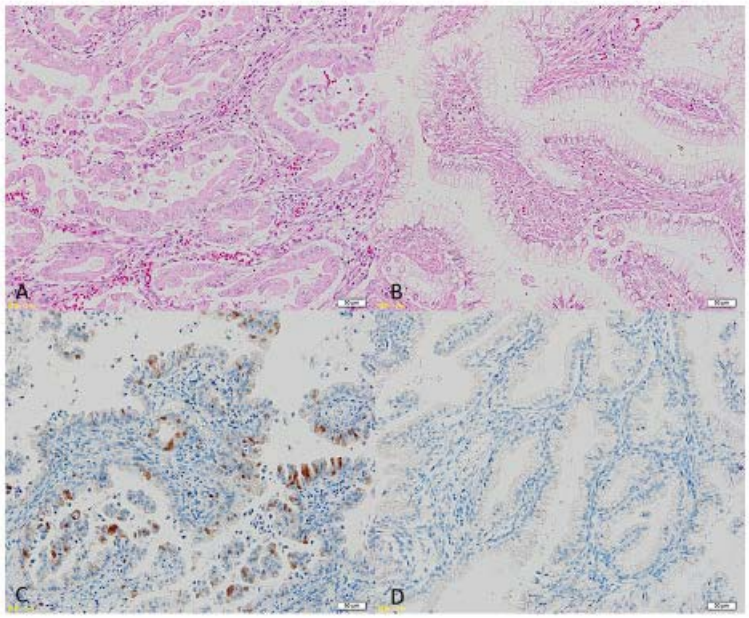

Figure. 4

Figure Legends

Fig. 1. Comparison of the 5-year survival rate by stage of cancer. The 5-year survival rate for patients with SCC and patients with AC/ASC did not differ significantly when cancer was stage I-II or stage III-IV. SCC: squamous cell carcinoma, AC: adenocarcinoma, ASC: adenosquamous carcinoma

Fig. 2. A) Comparison of the 5-year survival rate for patients with stage I-II cervical cancer who underwent surgery. The 5-year survival rate for patients with SCC and patients with AC/ASC did not differ significantly. B) Prognosis by initial treatment for patients with stage I-II AC/ASC of the cervix. Patients undergoing initial surgery had a significantly better prognosis that patients receiving radiation therapy (including CCRT) ($P < 0.02$).
SCC: squamous cell carcinoma, AC: adenocarcinoma, ASC: adenosquamous carcinoma, RT: radiation therapy, CCRT: concurrent chemotherapy and radiation therapy

Fig. 3. Cases where a different pathological diagnosis was made. Cancer previously identified as endometrioid AC was reclassified as usual-type endocervical AC. Results suggested that differentiation of usual-type endocervical AC lacking cytoplasmic mucins is difficult (mag x40 on left, x200 on right).

Fig. 4. Cases where differentiation of usual-type endocervical AC and gastric-type mucinous AC was difficult. A) Sites indicative of usual-type endocervical AC. HE staining, mag x200. B) Sites indicative of gastric-type mucinous AC. HE staining, mag x200. C) An AC component that was positive for P16 in some areas. Mag x200. D) An AC component that was weakly positive for HIK-1083. Mag x200.