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Clinical Features and Prognostic Factors of Cervical Clear Cell Adenocarcinoma: A Retrospective Analysis of 74 Cases from a Tertiary Hospital

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Abstract

The retrospective study aimed to analyze the clinical characteristics, primary treatment, and prognosis of cervical clear cell adenocarcinoma in a tertiary referral center. The medical data of cervical clear cell adenocarcinoma patients treated in our institution between 1993 and 2020 were reviewed. Their clinical characteristics and information on treatment and follow-up were collected. Seventy-four cases were included. Six early-stage patients successfully preserved their fertility. Forty-five patients underwent a radical hysterectomy. Patients with pathological risk factors all received adjuvant treatment including chemotherapy, radiotherapy, and chemoradiation. Fifteen patients without risk factors underwent surveillance and five patients received adjuvant chemotherapy for poorly differentiated disease. Twenty cases had radiation for primary treatment. Six of them underwent surgery after chemoradiotherapy, and five had pathological residual disease, including three who had pathological risk factors. The median follow-up interval was 36 months, with a 3-year OS and PFS rate of 82.4% and 81.4%, respectively. No recurrence or death was observed in patients with fertility-sparing treatment. FIGO stage was prognostic factors of PFS ($P = .001$) and OS($P = .006$) and lymph node status was that of PFS ($P = .023$). FIGO stage and lymph node status were prognostic factors for survival. Fertility-sparing treatment is a safe option for young patients in early stage. Early-stage patients without risk factors may benefit from postoperative surveillance. Occult tumor after chemoradiotherapy is common, and surgical resection is recommended when operable residual disease is detected.

Keywords

surgical procedures, operative, fertility, prognosis, chemotherapy, adjuvant, radiotherapy, adjuvant

Abbreviations

ADC, adenocarcinoma; ASC, adenosquamous carcinoma; CCAC, cervical clear cell adenocarcinoma; CCRT, concurrent chemoradiotherapy; CRT, chemoradiotherapy; DSI, deep stromal invasion; FIGO, The International Federation of Gynecology and Obstetrics; hr-HPV, high-risk human papillomavirus; LACC, locally advanced cervical cancer; LVSI, lymphovascular space invasion; NACT, neoadjuvant chemotherapy; OS, overall survival; PFS, progression-free survival; SCC, squamous cell carcinoma; TCT, Thinprep Cytology Test; HWWS, Herlyn–Werner–Wunderlich syndrome

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Introduction

CCAC, a rare variant of cervical ADC, accounts for 4% to 9% of all ADCs.[1,2] CCAC is significantly different from SCC and usual-type ADC in terms of etiology, clinical features, and prognosis. The vast majority of cervical cancers are associated with high-risk HPV infection, but only 20% of CCACs are reported to be HPV-associated[3] and several studies have

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reported that CCAC is not correlated with HPV infection.[4] This rare type of ADC is also considered to have a worse prognosis than SCC,[5] although comparisons of the survival outcomes of CCAC and HPV-associated ADC have yielded contradictory findings.[6,7] According to previous studies, the prognostic factors of CCAC include advanced cancer, tumor size, lymph node metastasis (LNM), nuclear atypia, and mitotic activity.[8–11] Nevertheless, large-scale studies to elucidate the characteristics and prognostic factors of CCAC are still lacking owing to the low incidence of this disease, and treatment modalities for CCAC are generally based on the data obtained for SCCs and ADCs.[9,12]

The aim of our Investigation is to summarize the clinical characteristics, primary treatment strategies, and outcomes of patients with CCAC from our institution. The findings will facilitate further clinical decision-making and are expected to serve as a beneficial supplement to the existing knowledge of this disease.

Materials and Methods

Study Population and Pathologic Review

Information on consecutive 79 patients diagnosed with CCAC and treated at a tertiary hospital between 1993 and 2020 was retrospectively collected. All patients had histopathologically confirmed CCAC identified using biopsy or surgical specimens, and all specimens underwent a second pathology review by two experienced pathologists. The diagnosis was established based on the morphologic and immunophenotypic features of clear cell carcinoma defined by the World Health Organization Classification of Tumors, 5th Edition.[13] Table 1 lists the immunohistochemical findings, and Figure 1 shows the microphotographs of representative cases. Detailed clinicopathological data were extracted from the electronic medical record system, including age, tumor stage, surgical extent, pathological results, details of radiation and chemotherapy, and follow-up information. We excluded three patients with tumors of mixed histology and two patients with tumors involving both the cervix and corpus, where we were unable to identify the primary origin.

Study Design

The FIGO staging of cervical cancer (2018) was used to revise the cervical cancer stage of patients.[14] Parametrial and surgical margin involvement, LNM, DSI, LVSI, and tumor diameter >4 cm were defined as risk factors. The follow-up time was defined as the interval between diagnosis and death or the last contact. Follow-up information was obtained in an outpatient setting or via telephone. For survival analysis, PFS was calculated from the beginning of treatment to the date of confirmed progression or death without progression. OS was calculated from the date of diagnosis to either the date of death or the latest date of confirmed survival.

Table 1. Immunohistochemical Findings of CCAC.

Immunohistochemical expression markers	Percentage of positivity
PAX8	97.3 (71/73)
Napsin A	74.3 (52/70)
HNF1β	97.2 (69/71)
WT1	0 (0/64)
ER	18.1 (13/72)
PR	9.7 (7/72)
p53, abnormal	15.1 (11/73)

Statistical Analysis

Data analysis was performed using SPSS software (version 26.0; IBM Corporation). All *P* values were two-sided, and *P* values less than .05 were considered statistically significant. The chi-square test and Fisher's exact test were used to assess differences in categorical data, and the Mann–Whitney *U* test was used to compare that in continuous data. Survival estimates were determined using the Kaplan–Meier method, and a comparison of groups was performed using the log-rank test. Univariate and multivariate survival analyses were performed using the Cox regression model.

Ethics Approval

The study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of our institution (approval number: S-K1388) on January 8th, 2021, with an exemption from the need to obtain informed consent. No specific consent was required for statistical analyses of the aggregated de-identified data. For this study, the raw data were first extracted from the hospital information system, and patient identities, including names, screening IDs, patient IDs, and mobile phone numbers, were de-identified. This retrospective study was conducted in accordance with the STROBE guidelines.[15]

Results

Clinical Manifestations

Seventy-four patients with CCAC were included in this retrospective cohort study, representing 7.5% of ADCs diagnosed during the study period. The median age at diagnosis was 46 years (range, 8-74 years). No patient had a history of intrauterine exposure to diethylstilbestrol. Clinical symptoms were observed in 97.3% of the patients, of which 25 presented with intermenstrual bleeding, 22 with postcoital vaginal bleeding, 14 with postmenopausal vaginal bleeding, 8 with abnormal vaginal discharge, 2 with abdominal pain, and 1 with lower-extremity edema. Two asymptomatic patients had an abnormal cervical appearance and were diagnosed during a health check-up.

Among the 18 patients who underwent a hr-HPV test as a screening method, 6 (33.3%) tested positive. In the TCT, 14 patients (66.7%) showed abnormal test results: the number of patients with atypical squamous cells of undetermined

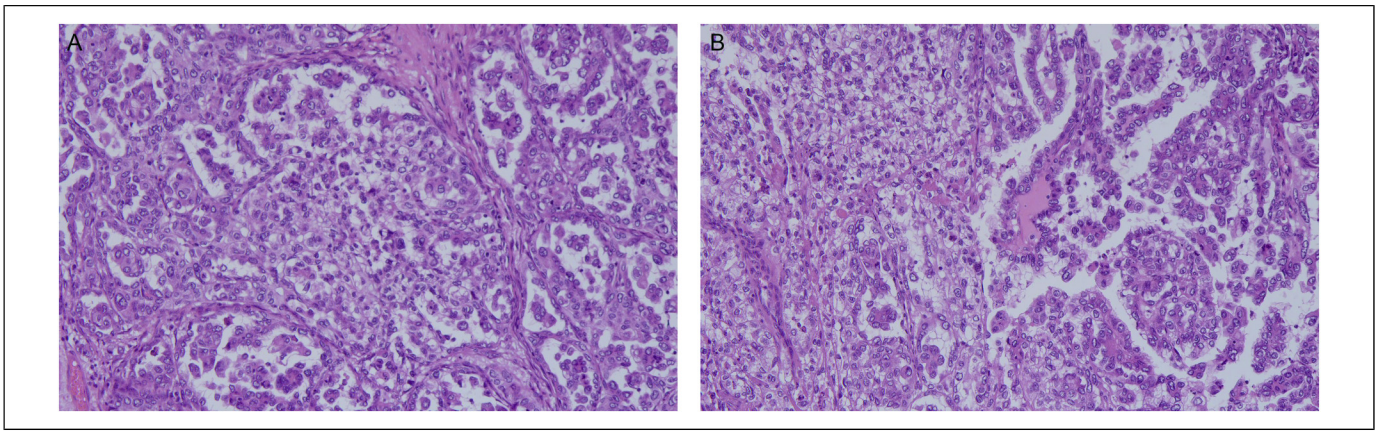

Figure 1. Micrographs of clear cell adenocarcinoma of cervix. The tumor has a tubulocystic and solid architecture of large polygonal and hobnail cells with an eosinophilic or clear cytoplasm. (A) 100× and (B) 100× (hematoxylin and eosin).

Table 2. FIGO 2018 Staging of 74 CACC Patients.

FIGO stage (2018)	*n* (%)
I	
IA1	2 (2.7)
IA2	1 (1.4)
IB1	12 (16.2)
IB2	18 (24.3)
IB3	9 (12.2)
II	
IIA1	4 (5.4)
IIA2	1 (1.4)
IIB	12 (16.2)
III	
IIIA	1 (1.4)
IIIB	1 (1.4)
IIIC1p	8 (10.8)
IIIC1r	3 (4.1)
IV	
IVB	2 (2.7)

Table 3. Surgical Extent of 53 Patients Receiving Surgeries as Primary Treatment.

Surgical extent	*n* (%)
RT + PLND[a]	5 (9.4)
Conization	1 (1.9)
Simple trachelectomy	1 (1.9)
Extrafacial hysterectomy	1 (1.9)
RH + PLND[b]	45 (84.9)

[a]Radical trachelectomy and pelvic lymphadenectomy.
[b]Radical hysterectomy and pelvic lymphadenectomy.

significance, low-grade squamous intraepithelial lesions, high-grade squamous intraepithelial lesions, atypical glandular cells, and adenocarcinoma were five, one, five, two, and one, respectively. Twenty-five patients (33.8%) had elevated serum CA125. Two patients had congenital anomalies, with one presenting as HWWS, and another presenting as uterus didelphys, double cervix, double vagina, vaginal atresia, and imperforate anus. After restaging with 2018 FIGO staging system, the number of patients in stage I, II, III, and IV were 42, 17, 13, and 2, respectively. The detailed distribution of FIGO stage at diagnosis is presented in Table 2.

Surgical Management as Primary Treatment

Overall, seven patients underwent fertility-sparing surgeries, including two patients who underwent conization or simple trachelectomy (Table 3): one 20-year-old patient underwent cervical polypectomy and was diagnosed as CCAC; the patient then underwent conization that showed benign pathological results; she underwent three cycles of chemotherapy and routine follow-up thereafter. Another 8-year-old patient underwent a cervical tumor resection with clear margins and was diagnosed as CCAC; the tumor was grossly invisible after the resection; the patient then underwent two cycles of chemotherapy followed by simple trachelectomy, and the final histopathological result showed a residual lesion measuring 0.3 mm; the patient underwent periodic surveillance postoperatively. In one case where fertility preservation was unsuccessful, the patient showed a node-positive status and received CRT postoperatively.

Extrafacial hysterectomy was performed for one patient with FIGO stage IA1 disease. Forty-five patients underwent radical hysterectomy with pelvic lymphadenectomy, and their FIGO stages were as follows: IA2-IB3, 33 patients; IIA1-IIA2, 5 patients; and IIIC1p, 7 patients (IB1-IIA2 according to FIGO 2009). NACT was administered to six patients with stage IB3-IIA2 disease.

DSI was detected in 20 patients, including stage IB1, IB2, IB3, IIA, and IIIC1p disease in one (12.5%), six (35.3%), four (57.1%), four (80.0%), and five patients (71.4%), respectively. Five patients showed LVSI, with three (7.7%) showing stage IA–IIA disease and two (28.6%) showing stage IIIC1p disease ($P = .038$). Nine patients had pelvic LNM, and the average diameter of the tumor in these patients was 5.9 ± 3.0 cm; the average diameter in patients with node-negative

disease was 3.0 ± 1.3 cm ($P = .003$). None of the patients presented with para-aortic LNM, parametrium, or surgical margin involvement.

Fifteen patients without pathological risk factors did not receive postoperative adjuvant treatment. Five patients received platinum-based adjuvant chemotherapy for poorly differentiated disease. Twenty-five patients with at least one risk factor received external beam radiotherapy ± concomitant chemotherapy ± brachytherapy as adjuvant treatment.

Radiotherapy as Primary Treatment

Twenty patients received radiotherapy with or without chemotherapy as the primary treatment. Three underwent only radiotherapy because of their deteriorated hepatorenal function. The distribution of cases by FIGO stage was as follows: one in IB1 because of the patient's refusal to undergo surgery, one in IB3, twelve in IIB, one in IIIA, one in IIIB, three in IIIC1r, and one in IVB. Concurrent chemotherapy regimens consisted of single-agent chemotherapy (concomitant weekly cisplatin or paclitaxel for patients with impaired renal function) and platinum-based combination chemotherapy. Nine and eight patients received single-agent and multiagent chemotherapy, respectively.

Six patients received surgery after CRT due to suspected residual lesion. The average interval between the last day of CRT and the date of surgery was 2.9 ± 0.4 months. The FIGO stage, surgical extent, and postsurgical pathologic features of these patients are shown in Table 4.

One patient was complicated with thrombophilia presented with deep venous thrombus, excessive vaginal blood loss during anticoagulation, and ventricular mural thrombus. She received palliative care for severe complications and poor general condition.

Oncological and Obstetrical Outcomes

The median follow-up interval was 36 months (range, 1-195 months). Fifteen progressions were detected, and the 3-year PFS rate was 81.4% (Figure 2). The median time to recurrence was 11 months (range 4-69 months). Thirteen patients died, including four cases of progressive disease, and one patient who died of stroke without evidence of progression, yielding a 3-year survival rate of 82.4%. The median interval between the detection of progression and the date of death was 4 months (range, 1-26 months). The detailed clinical features of recurrent and persistent disease are presented in Table 5.

After a median follow-up period of 81 months (range, 18-181 months), no recurrence or death was detected in six patients who successfully completed fertility-preserving treatment. Two patients attempted to conceive, and they both achieved one pregnancy. Two babies were born (one preterm and one full-term delivery).

Univariate analysis revealed that the FIGO stage was a significant prognostic factor for OS and PFS (Table 6 and Figures 3 and 4). Patients with early-stage disease (IA–IIA) showed better OS ($P = .006$) and PFS ($P = .001$) than advanced-stage patients (IIB–IVB). Patients with LNM had a worse PFS ($P = .023$). However, no significant prognostic factors were identified in the multivariate analysis.

Table 4. Detailed Clinical and Pathological Features of CCAC Receiving Surgery After Chemoradiation.

FIGO stage (2018)	Surgical extent	Postoperative pathological characteristics
IB3	EH[a]	Less than 50% stromal invasion
IIB	RH[b]	Less than 50% stromal invasion
IIB	EH	Pathological complete response
IIB	EH	DSI, positive margin
IIB	PE[c]	Invasion of pelvic sidewall, LVSI
IIIA	RH	LNM, LVSI

[a]Extrafascial hysterectomy.
[b]Radical hysterectomy.
[c]Pelvic exenteration.

Discussion

CCAC is a rare histological type of ADC and appears to be unrelated to hr-HPV infections. However, few studies have explored the clinicopathological characteristics and prognostic factors of CCAC owing to its low incidence. Treatment of the disease still follows the patterns employed for SCC and ADC. Herein, we focus on CCAC cases in a large tertiary hospital and draw interesting conclusions.

Screening Methods

According to previous studies, the association of hr-HPV with the incidence of CCAC is debatable, and some studies have indicated

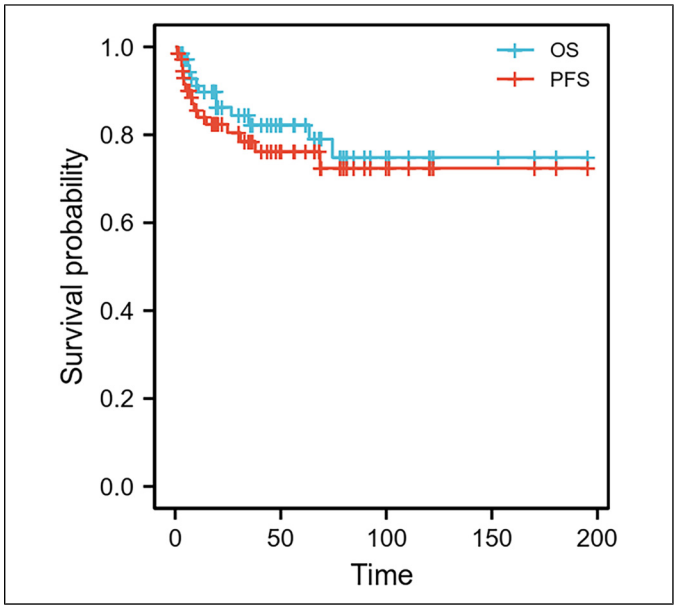

Figure 2. Survival curves of the CCAC cohort.

Table 5. Detailed Characteristics of Patients with Persistent or Recurrent CCAC.

No	FIGO stage	Primary treatment modality	Response to treatment[f]	PFS	Recurrence	Cancer-related death	OS
1	IIIC1p	S[a] + CRT[b]	CR[g]	8.1	Y	Y	26.6
2	IIIC1p	NACT[c] + S + CRT	CR	37.9	Y	Y	63.5
3	IB2	S + CT[d]	CR	4.9	Y	Y	7.2
4	IB2	S	CR	4.2	Y	Y	19.4
5	IIB	CRT + S + CT	CR	14.7	Y	Y	19.5
6	IIB	RT[e]	CR	9	Y	Y	10.1
7	IIIC1r	CRT	CR	30.9	Y	Y	34.9
8	IVB	CRT	CR	68.6	Y	Y	74.5
9	IIIC1p	NACT + S + CRT	CR	24.8	Y	N	153.2
10	IB2	S + CRT	CR	10.7	Y	N	36
11	IIIA	CRT + S + CRT	CR	7.9	Y	N	61.7
12	IIB	CRT	PD[h]	2.7	N	Y	6.8
13	IIB	CRT	PD	2.9	N	Y	4
14	IIB	CRT	PD	2.1	N	Y	6.1
15	IVB	Palliative care	PD	1	N	Y	11

[a]Surgery.
[b]Chemoradiotherapy.
[c]Neoadjuvant chemotherapy.
[d]Chemotherapy.
[e]Radiotherapy.
[f]Response to treatment measured using RECIST v1.1.
[g]Complete response.
[h]Progressive disease.

that 0% to 30% of CCAC cases are hr-HPV positive.[3,16–18] Our data is consistent with these previous findings. Pirog et al argued that hr-HPV testing and HPV vaccination would not help prevent this rare subtype of cervical cancer.[4] Thomas reported an abnormal Pap smear in 18% of CCAC patients.[12] Our study revealed a higher incidence of abnormal TCT findings (66.7%). The reason for this discrepancy may be that TCT provides more effective detection of cervical lesions than conventional smears.[19] Since the majority of patients were symptomatic at diagnosis, and established and effective screening methods are still lacking, patients' symptoms are of paramount importance. Thus, invasive diagnostic methods such as cervical biopsy, endocervical curettage, or surgical resection should be considered in patients with suspected cervical cancer.

Genitourinary Malformation

Congenital anomaly of the female genital tract has a prevalence of 4% to 7% in the general population.[20] HWWS is a rare anomaly characterized by uterus didelphys, blind hemivagina, and ipsilateral renal agenesis and accounts for 7.1% of all abnormalities of female genital tract.[21] The incidence of HWWS is 1.4% in our cohort. Herbst et al reported that the prevalence of congenital malformations in cervical or vaginal clear cell carcinoma was 6%.[11] Another retrospective study of 36 women reported that 69% of the patients with genitourinary malformations had adenocarcinoma of the lower genital tract.[22] Therefore, it is conceivable that congenital anomalies are linked to an elevated risk of primary malignancies. According to a theory put forth by Sporri et al, the Müllerian epithelium may become vulnerable to carcinogenic substances due to teratogenic effects,[23] and Knudson's two-hit hypothesis of carcinogenesis was best illustrated by the connection between teratogenesis and oncogenesis.[24] But there is no genetic proof thus far. In individuals with genitourinary abnormalities, it is necessary to determine their genetic profile and probability of developing cancer.

Fertility-preserving Surgery

Previously reported cohorts seemed to show a bimodal distribution of the age of onset, with twin peaks at 17 to 37 years and 44 to 88 years.[25,26] Young patients with CCAC usually wished to preserve their fertility; however, only the histological characteristics of SCC, ADC, or ASC are incorporated into the widely accepted criteria for radical trachelectomy. CCAC is generally considered an aggressive subtype, and fertility-sparing surgery has not been carefully considered and further explored in this subtype.[27] According to previous studies, all patients were stage IB, and no recurrence or death was observed in these reports.[28–31] But the data did not mention the obstetric outcomes. In our population, patients who underwent fertility preservation had stage IA–IB disease. No recurrence or death was detected, and the obstetric outcomes were quite favorable, with a pregnancy rate of 100%, live birth rate of 100%, and preterm birth rate of 50%. The fertility-sparing treatment in young patients with early-stage CCAC could be safe and feasible. Nevertheless, we still recommend prudent fertility preservation because of the limited knowledge on this issue.

Postoperative Adjuvant Treatment

Previous studies have reported that adjuvant treatment did not affect survival outcomes in early-stage cervical cancer

Table 6. Univariate and Multivariate Analyses of Clinicopathologic Parameters on PFS and OS in CCAC Patients.

	Univariate analysis				Multivariate analysis			
	OS		PFS		OS		PFS	
Variables	HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P*
FIGO stage								
IA–IIA	1		1		1		1	
IIB–IVB	5.037 (1.577-16.090)	.006*	6.607 (2.123-20.562)	.001*	3.298 (0.368-29.595)	.286	3.369 (0.375-30.231)	.278
LNM								
No	1		1		1		1	
Yes	1.930 (0.374-9.955)	.432	4.600 (1.230-17.198)	.023*	0.680 (0.061-7.521)	.753	1.590 (0.177-14.268)	.678
Tumor size								
<4 cm	1		1					
≥4 cm	1.682 (0.564-5.012)	.351	1.152 (0.417-3.180)	.785				
LVSI								
No	1		1					
Yes	2.342 (0.452-12.122)	.310	2.243 (0.451-11.140)	.323				
DSI								
No	1		1					
Yes	1.106 (0.247-4.950)	.895	1.744 (0.361-8.423)	.489				

*$P < 0.05$.

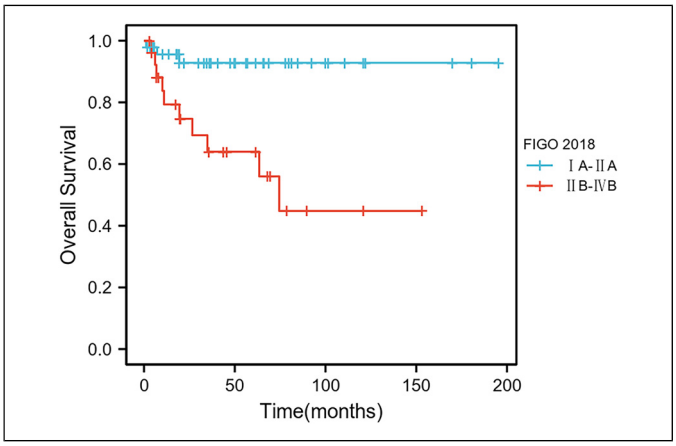

Figure 3. Kaplan–Meier survival curve of OS comparing IA–IIA and IIB–IVB ($P = .002$).

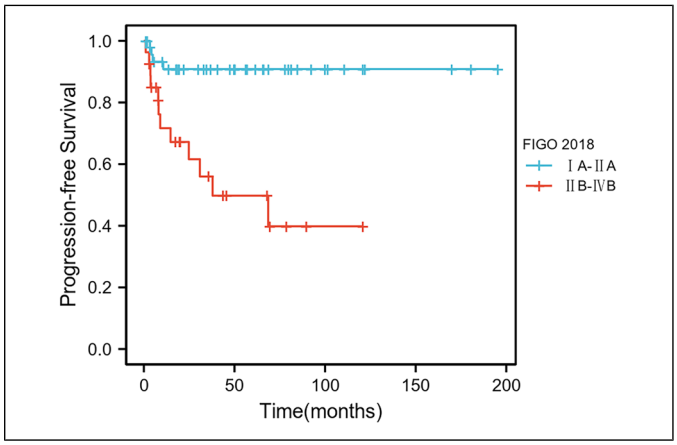

Figure 4. Kaplan–Meier survival curve of PFS comparing IA–IIA and IIB–IVB ($P < .001$).

without any pathological risk factors.[12] Similar results have been documented for ADC.[32] Early-stage ADC without pathological risk factors had a favorable 5-year OS rate of 80.8%.[33] In our population, patients with early-stage CCAC without adverse risk factors who underwent postoperative surveillance had a 3-year OS and PFS rate of 92.9% and 84.0%, respectively. Therefore, we recommend surveillance other than adjuvant treatment for early-stage CCAC without risk factors.

Adopting Platinum-based Multiagent Chemotherapy During Radiotherapy

Weekly cisplatin plus radiotherapy is the standard regimen for advanced cervical cancer. Previous studies have evaluated whether platinum-based doublet therapy improves survival compared to weekly cisplatin plus radiotherapy. Lee et al reported that in cervical cancer with pelvic LNM, platinum-based polychemotherapy as combination chemotherapy conferred favorable survival in comparison with weekly cisplatin, reducing the risk of recurrence by 77%.[34] A systematic review supported that in LACC patients who underwent CRT, cisplatin-based doublets had improved OS, PFS, and local control in comparison with concomitant cisplatin chemotherapy.[35] The combination strategy will likely lead to increased cytotoxicity and radiosensitization compared to cisplatin as a single agent. Since ADC is not as radiosensitive as SCC, CCAC as a rare subtype of ADC may benefit from platinum-based doublet therapy plus radiotherapy.[36–42]

Uncertainty about Radiosensitization of CCAC

The prevalent treatment of CCAC is generally in accordance with the guidelines of SCC and ADC. However, the response of ADC to radiation remains controversial. A retrospective analysis reported a 5-year OS rate of 20.2% for ADC of stage IIIB, which was significantly worse than that for SCC.[43] Another study by Shimada et al revealed that adjuvant radiotherapy resulted in a higher recurrence rate in ADC than in SCC (24.6% vs 10.5%).[44] Another study showed that in IB-IIA cervical cancer patients who received radiation or CCRT for adjuvant treatment, ADC histology was associated with worse survival outcome.[45] Previous studies have reported that among patients who show clinically and radiologically complete remission after CRT, 30% had pathological residual lesions. The proportion of residual disease was even higher in the ADC group, reaching 50%.[46,47] Another study found that 27.4% of ADCs had clinically or radiologically visible lesions after CRT, and 64.1% proved to have pathological residual disease.[48] Our results showed that in patients who underwent surgical resection after definite CRT, 83.3% had pathological residual disease, including 50.0% who had risk factors. It is consistent with these previous findings but shows a relatively higher proportion of residual disease. This may be attributed to the small number of patients, which limited the statistical power, and the resistance of CCAC to radiotherapy or chemotherapy.[49,50] Therefore, we recommend comprehensive clinical and radiological assessment after CRT, and close attention should be paid to surgical treatment when residual disease is suspected.

Limitations

This study had several limitations. First, an unmeasured bias exists because of the retrospective nature of the study. Second, the small number of patients limits further subgroup analysis and decreases the statistical power. Third, prolonged follow-up is needed to observe the long-term oncological and obstetrical outcomes.

Conclusion

To our knowledge, this is one of the largest studies to date to evaluate the clinical features and survival outcomes of CCAC. The conventional screening methods are not effective in CCAC, so invasive methods are necessary for diagnosis in suspected CCAC patients. The FIGO stage and lymph node status are prognostic factors for survival outcomes. Fertility-sparing surgery may be a safe option for early-stage CCAC in young patients. Early-stage CCAC patients without pathological risk factors may benefit from postoperative surveillance. We highlight the presence of occult tumor after definitive CRT. Post-CRT evaluation is crucial, and we recommend surgical resection when residual disease is detected.

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Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethics Approval

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of Peking Union Medical College Hospital (approval number: S-K1388) on January 8th, 2021, with an exemption from informed consent. The location of review board is in Peking Union Medical College Hospital, No.1 ShuaiFuYuan, Dongcheng District, Beijing, China. No specific consent is needed for statistical analyses of aggregated deidentified data. For this study, the raw data were first extracted from HIS, and patients' identities, including names, screening IDs, patient IDs, and mobile phone numbers, were de-identified.

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