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ORIGINAL RESEARCH

Factors Associated with Patient Survival in Clear Cell Adenocarcinoma of the Cervix: A Single-Center Experience in China

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Purpose: Clear cell adenocarcinoma of the cervix (CCAC) is a rare pathological type of cervical cancer. This study aimed to report our clinical experience with CCAC treatment and analyze the factors associated with patient survival.

Patients and Methods: This single-center study included patients diagnosed with CCAC and treated between 01/2003 and 12/2017 at the Obstetrics and Gynecology Hospital of Fudan University. The patients diagnosed with CCAC that underwent radical resection were included. The Kaplan–Meier method and multivariable Cox regression analysis were performed to determine factors associated with patient survival.

Results: Fifty-four patients were included. None were exposed to diethylstilbestrol. The median follow-up was 96 (13.0, 120.0) months. The median recurrence-free survival (RFS) and overall survival (OS) were 68 and 78 months, respectively. Positive pelvic lymph nodes (HR=2.87, 95% confidence interval [CI] 1.14–7.22, P=0.03), tumor size >4 cm (HR=3.31, 95% CI 1.35–8.12, P=0.01), International Federation of Gynecology and Obstetrics (FIGO) IB2-IIA2 stage (HR=2.49, 95% CI 1.56–3.99, P=0.02), and post-operative therapy (HR=1.73, 95% CI 1.07–2.81, P=0.03) were associated with OS. Multivariable analysis showed that FIGO stage IB2-IIA2 (HR=2.36, 95% CI 1.52–3.68, P<0.01) and lymph node status (HR=3.05, 95% CI 1.12–8.28, P=0.03) were independently associated with OS.

Conclusion: Advanced FIGO stage and positive lymph node status are independently associated with shorter survival in patients with CCAC who were not exposed to diethylstilbestrol. After surgery, chemotherapy and concurrent chemoradiotherapy were not independently associated with the prognosis of patients with CCAC.

Keywords: uterine cervical neoplasm, clear cell adenocarcinoma of the cervix, radical hysterectomy, chemoradiotherapy

Introduction

Clear cell adenocarcinoma of the cervix (CCAC) is a rare pathological type of cervical cancer and occurs mainly in women with a history of intrauterine exposure to diethylstilbestrol (DES).[1] Indeed, a case-control study in 1971 confirmed the relationship between intrauterine exposure of DES and CCAC occurrence.[2] In women exposed to DES, the incidence of CACC is approximately 1.6/1000 from birth to 39 years of age.[3] CCAC accounts for 4%-9% of cervical adenocarcinomas in patients not previously exposed to DES.[1] High-risk human papillomavirus (HPV) is associated with 64% and 73% of cervical adenocarcinomas (AC) and squamous cell carcinomas (SCC), respectively.[4] On the other hand, high-risk HPV is found in only 20% of patients with CCAC.[5]

Radical surgery is the standard and preferred treatment option for CCAC.[1] Patients with tumor diameter >4 cm, International Federation of Gynecology and Obstetrics (FIGO) stage IIA2-IV disease, pelvic lymph node (PLN) metastasis, and endometrial metastasis could benefit from platinum-based chemotherapy and radiotherapy in addition to surgery.[1,6] Recurrence after adjuvant therapy is higher in CCAC compared with SCC (25% vs 11%).[7] Consequently, the prognosis of CCAC is worse than for AC and SCC, with 5-year survival rates of 67%, 77%, and 80%, respectively.[8]

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To date, only case reports and small case series have implied that fertility-preserving treatments are feasible in patients with early-stage CCAC. For example, Singh et al[9] reported one patient who received neoadjuvant carboplatin and paclitaxel, underwent laparoscopic pelvic lymphadenectomy and vaginal radical trachelectomy, and received adjuvant carboplatin and paclitaxel; in this patient, the uterus could be conserved. In addition, Jiang et al[10] reported three patients who underwent fertility-preserving treatments for CCAC. Recently, a 6-year-old CCAC case was treated primarily with electrosurgical biopsy of the polypoid mass under hysteroscopy, followed by CT without traditional treatment, suggesting a novel treatment option for young CCAC cases.[11]

The sparsity of clinical data describing CCAC without DES exposure indicates that further trials are required to characterize this malignancy. Therefore, the present study aimed to assess the clinical characteristics, surgical treatment methods, and prognosis of patients with CCAC without a history of DES exposure.

Patients and Methods

Patients

This retrospective study included patients diagnosed with CCAC and treated between January 2003 and December 2017 at the Gynecology Department of the Obstetrics and Gynecology Hospital of Fudan University. The inclusion criteria were 1) diagnosis of CCAC by histopathology, 2) radical surgery (radical hysterectomy [Piver type III]) or radical trachelectomy + pelvic lymph node lymphadenectomy ± para-aortic lymphadenectomy), and 3) no history of DES exposure. The exclusion criteria were 1) failure to complete postoperative adjuvant therapy, 2) a history of associated other malignant tumors, or 3) failure to complete follow-up. This study was approved by the ethics committee of the Obstetrics and Gynecology Hospital of Fudan University (No. 2019–71). The patients had signed informed consents to use medical history and follow-up data, and the study complied with the Declaration of Helsinki.

Treatments

All the patients underwent radical surgery, Piver type III hysterectomy, or radical trachelectomy + pelvic lymph node lymphadenectomy ± para-aortic lymphadenectomy. High-risk factors after surgery were parametrial involvement, lymph node metastasis, or positive resection margin.[12] Intermediate-risk factors included clinical tumor diameter, histology, lymph-vascular space invasion (LVSI), and depth of stromal invasion.[12] Postoperative adjuvant therapy was required in the presence of at least one high-risk factor or at least two intermediate-risk factors.

The adjuvant chemotherapy regimen was platinum-based intravenous chemotherapy, at 3-week intervals, for four courses. The concurrent chemoradiation therapy (CCRT) regimen included a total dose of radiotherapy of 45 Gy, administered 5 times a week at 1.8 Gy (25 times per treatment course) and cisplatin at 40 mg/m^2, as intravenous chemotherapy every week. The selection of the specific adjuvant treatment was based on the high- and intermediate-risk factors and the clinician's judgment.

Data Collection and Definitions

Clinical data were collected from the hospital's electronic database, including age, menopausal status, symptoms, parity, Papanicolaou test, HPV infection, family history of cancer, history of ovarian cysts, CA125 serum levels before the operation, FIGO stage, surgical methods, lymph node metastasis, depth of stromal invasion, local invasion, distant metastasis, and postoperative treatments. The staging was based on the 2009 FIGO staging system for cervical cancer,[13] but the patients were re-staged according to the new FIGO system of 2018.[14]

Outcomes and Follow-Up

All patients were followed up every 3–4 months in the first 2 years, every 6 months in years 3–5, and yearly after that. The follow-up period was defined as the time interval between the date of surgery and death or the last follow-up. Recurrence-free survival (RFS) and overall survival (OS) were determined from the date of surgery to disease recurrence or death, respectively. The follow-up was censored in June 2019.

Statistical Analysis

SPSS 26.0 (IBM Corporation, Armonk, NY, USA) was used for statistical analysis. Normally distributed (based on the Kolmogorov–Smirnov test) continuous data were expressed as mean ± standard deviation, and non-normally distributed continuous data as median (range or IQR). Categorical data were expressed as numbers (%). Survival curves were plotted by the Kaplan-Meier method and tested using the Log rank test. Univariable and multivariable Cox regression analyses were performed. $P<0.05$ was considered statistically significant.

Results

Characteristics of the Patients

Fifty-four patients were diagnosed with CCAC and treated surgically during the study period. None of the patients had a history of exposure to DES. The median age at diagnosis was 46.5 (13–72) years. The median follow-up was 96 (13–120) months. Twenty-eight patients, including 20 who died and eight still alive, had a recurrence. The age distribution is shown in Figure 1. The patients presented with symptoms of irregular bleeding (46/54, 85.19%), vaginal discharge (6/54, 11.11%), and post-coital bleeding (2/54, 3.70%). Thirty-six patients (36/54, 66.67%) were premenopausal at diagnosis, and 22 (22/54, 40.74%) were nulliparous. Pap tests were abnormal in only seven patients, including two with high-grade squamous intraepithelial lesions (2/54, 3.70%), one with low-grade squamous intraepithelial lesions (1/54, 1.85%), and four with atypical squamous cells of undetermined significance (4/54, 7.41%). The HPV test was performed for these seven patients, all of whom showed negative results. The clinical data are summarized in Table 1.

Characteristics of the Tumors

The median tumor size was 3.5 (0.7–8) cm. Forty-one patients had FIGO stage I CCAC (41/54, 75.93%; 6, 23, and 12 cases had stage IA2, IB1, and IB2 lesions, respectively), and 13 patients had stage II CCAC (13/54, 24.07%; 7 and 6

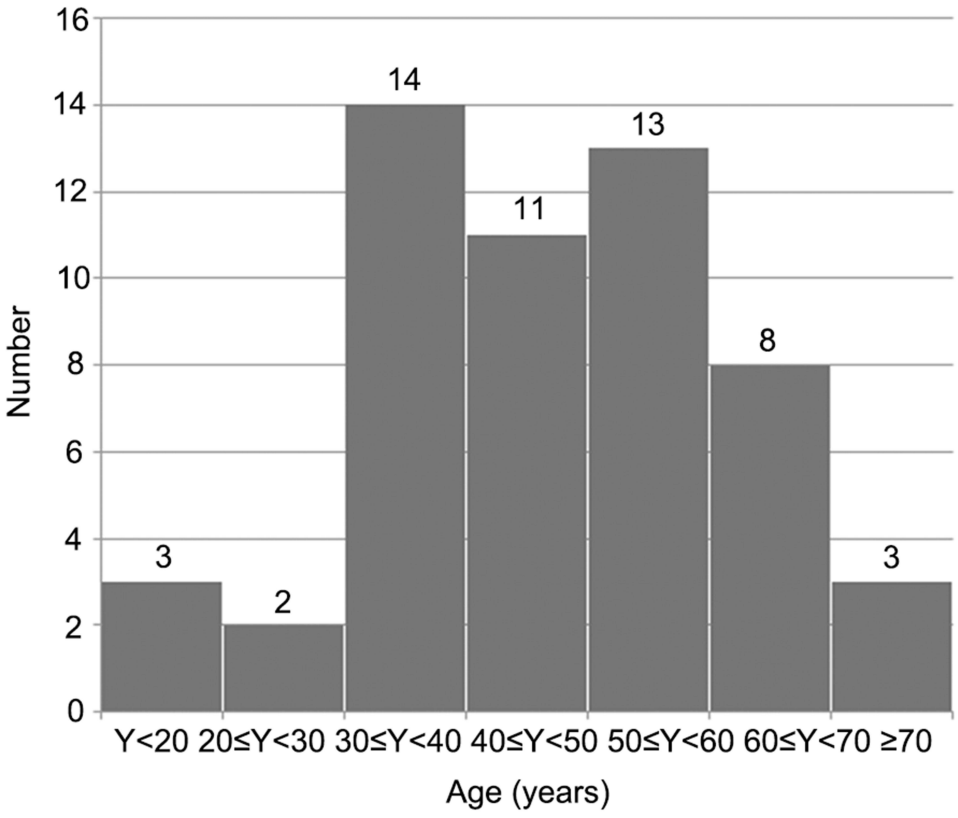

Figure 1 Age distribution of patients with clear cell carcinoma of the cervix (n=54).

Table 1 Characteristics and Outcome of Patients with CCAC (n=54)

Characteristics	N (%)
Age (years), median (range)	46.5 (13, 72)
Main complaints, n (%)	
Irregular bleeding	46 (85.19)
Vaginal discharge	6 (11.11)
Post-coital bleeding	2 (3.70)
Menopausal state, n (%)	
Premenopausal	36 (66.67)
Postmenopausal	18 (33.33)
Parity, n (%)	
Nulliparous	22 (40.74)
Parous	32 (59.26)
Pap test, n (%)	
Abnormal	7 (12.96)
Normal	47 (87.04)
HPV infection, n (%)	
Positive	0 (0.00)
Negative	7 (12.96)
Undetected	47 (87.04)
Family history of cancer, n (%)	
Yes	10 (18.52)
No	44 (81.48)
FIGO stage (2009), n (%)	
IA2	6 (11.11)
IB1	23 (42.60)
IB2	12 (22.22)
IIA1	7 (12.96)
IIA2	6 (11.11)
Surgery type, n (%)	
RH+ PLA +BSO	36 (66.67)
RH+PLA+BSO+PALA	7 (12.96)
RH+PLA+SO	6 (11.11)
RT+PLA+SO	1 (1.85)
RH+PLA+BSO+OM	3 (5.56)

(*Continued*)

Table 1 (Continued).

Characteristics	N (%)
RH+PLA++PALA+BSO+OM	1 (1.85)
Tumor size, n (%)	
≤4 cm	18 (33.33)
>4 cm	36 (66.67)
Lymph node metastasis, n (%)	
Positive	17 (31.48)
Negative	37 (68.52)
Depth of stromal invasion, n (%)	
≤2/3	43 (79.63)
>2/3	11 (20.37)
LVSI, n (%)	
Positive	13 (24.07)
Negative	41 (75.93)
Local invasion and distant metastasis, n (%)	
Vaginal vault invasion	6 (11.11)
Ovarian metastasis	2 (3.70)
Omentum metastasis	1 (1.85)
Postoperative therapy, n (%)	
No therapy	5 (9.26)
Chemotherapy	18 (33.33)
Radiotherapy	5 (9.26)
CCRT	26 (48.15)

Abbreviations: CCAC, clear cell carcinoma of the cervix; Pap test, Papanicolaou test; HPV, human papillomavirus; FIGO, International Federation of Gynecology and Obstetrics; RH, radical hysterectomy; PLA, pelvic lymphadenectomy; BSO, bilateral salpingo-oophorectomy; SO, suspension of the ovary; PALA, para-aortic lymphadenectomy; RT, radical trachelectomy; OM, omentectomy; LVSI, lymphatic vascular space invasion; CCRT, concurrent chemoradiation therapy.

cases had stage IIA1 and IIA2 lesions, respectively). All patients underwent CA125 examination before surgery, and normal results were obtained (all <35 U/mL). The histopathological data are summarized in Table 1. All patients were re-staged according to the 2018 FIGO system (Table 2).

Treatments

Fifty-three patients (53/54, 98.15%) underwent a radical hysterectomy, and only one patient (1/54, 1.85%) underwent fertility-preserving treatment (radical trachelectomy); seven patients (7/54, 12.96%) had ovarian preservation. Pelvic

Table 2 The Stage Shift Between FIGO 2009 and 2018 Staging Systems

	FIGO 2009, n	FIGO 2018, n (%)							
		IA2	IB1	IB2	IB3	IIA1	IIA2	IIIC1	IIIC2
IA2	6	6 (100.0)							
IB1	23		10 (43.48)	8 (34.78)				5 (21.74)	
IB2	12				7 (58.33)			3 (25.00)	2 (16.67)
IIA1	7					4 (57.14)		2 (28.57)	1 (14.29)
IIA2	6						2 (33.33)	3 (50.00)	1 (16.67)

Abbreviation: FIGO, International Federation of Gynecology and Obstetrics.

lymphadenectomy was performed in all patients, yielding a median of 21 (10–33) nodes. Para-aortic lymphadenectomy was performed in eight cases (8/54, 14.81%), yielding a median of 4.6 (3–5) nodes. Omentectomy and omentum biopsy were performed in four patients (4/54, 7.41%). Pathological examination showed PLN metastasis in 17 patients (17/54, 31.48%), deep cervical stromal invasion in 11 (11/54, 20.37%), LVSI in 13 (13/54, 24.07%), vaginal vault invasion in six (6/54, 11.11%), ovarian metastasis in two (2/54, 3.70%), and omentum metastasis in one (1/54, 1.85%). No metastasis was detected in the para-aortic lymph nodes.

Only one patient aged 19 years underwent fertility-preserving surgery and received chemoradiation post-surgically. Preventive ureteral stent placement was performed in six patients. Blood transfusion was performed in four patients with intraoperative bleeding exceeding 800 mL. The average bleeding volume was 312 mL. The average operation time was 195 min. Among these patients, 4 (4/54, 7.41%) underwent laparotomy, and 50 (50/54, 92.59%) had laparoscopic treatment. Forty-nine patients received adjuvant radiotherapy, chemotherapy, or CCRT.

Survival Data

The 5-year RFS and OS rates among all 54 patients were 66% and 72%, respectively. The median OS and RFS were 78 and 68 months, respectively. The median OS in patients with negative and positive PLN was 100 vs 45 months (P=0.02), respectively (Figure 2A). The median RFS in patients with negative and positive PLN was 90 vs 39 months (P=0.02), respectively (Figure 2B). The median OS in patients with chemotherapy (CT) (n=18) and concurrent chemoradiotherapy (CCRT) (n=26) was 68 vs 52 months (P=0.21), respectively (Figure 2C). The median RFS in patients with CT (n=18) was not reached, while patients who received CCRT had a median RFS of 48 months (n=26) (P=0.19) (Figure 2D). The no-therapy and radiotherapy groups were not included because of the small number of patients. There were no differences in OS and RFS in patients with CCAC who underwent CT vs CCRT after radical surgery (P>0.05) (Figure 2).

Factors Affecting Patient Survival

Table 3 shows the results of univariable and multivariable Cox analyses. FIGO stage (P<0.01, HR=2.36, 95% CI:1.52–3.68) and lymph node status (P=0.03, HR=3.05, 95% CI: 1.12–8.28) were independently associated with poor survival.

Discussion

This study suggested that FIGO stage and lymph node status were independently associated with survival in patients with CCAC. Adjuvant treatments (chemotherapy and chemoradiation) after radical surgery might not affect OS and RFS in CCAC, but further studies are needed for confirmation.

The etiology and pathogenesis of CCAC are not completely understood. Studies suggested that many factors, including genetic factors, instability of microsatellite repeats, mutations in the p53 gene, overexpression of the BCL-2 gene, and even cervical endometriosis, contribute to the occurrence of CCAC.[15,16] CCAC is characterized by irregular vaginal bleeding, most of the endogenous type.[17] Therefore, CCAC is difficult to detect by gynecological examinations or Pap tests. Thomas et al[18] reported that only 18% of patients with CCAC had abnormal cervical cytology. Whether

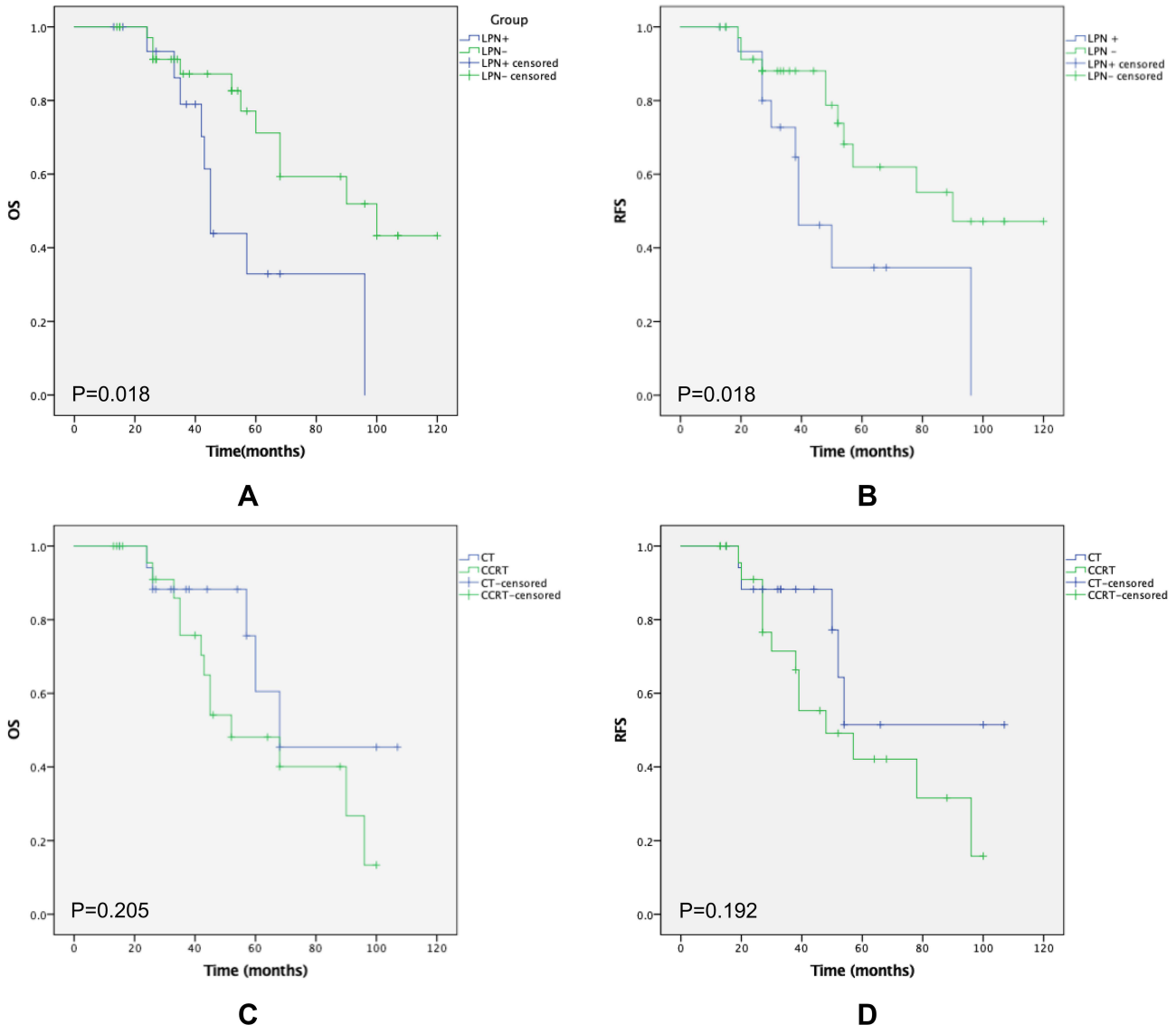

Figure 2 Kaplan–Meier curves for overall survival (OS) and recurrence-free survival (RFS) in patients with cervical clear cell carcinoma of the cervix. (**A**) Median OS times in patients with negative pelvic lymph nodes (PLN) and positive PLN (P=0.018). (**B**) Median RFS times in patients with negative PLN and positive PLN (P=0.018). (**C**) Median OS times in patients administered chemotherapy (CT) (n=18) and concurrent chemoradiotherapy (CCRT) (n=26) (P=0.205). (**D**) Median RFS times in patients administered CT (n=18; not reached) and CCRT (n=26) (P=0.192).

CCAC is associated with HPV infection remains controversial. Recent studies have shown that CCAC might not be associated with high-risk HPV infection.[19,20] In the present study, there were seven patients with abnormal cervical screening results, but these seven patients were negative for HPV and had normal preoperative CA125 levels. These findings suggested that CCAC might not be effectively detected using tumor markers, although further investigation is required for confirmation. Kotowicz et al[21] considered serum CA125 an independent prognostic factor in AC. CA125 elevation might not be notable in this study because of the early stage of the included patients. Whether there is a correlation between CCAC and CA125 levels requires further large sample studies.

The 5-year OS in the present study was 72%, which is consistent with the previously reported survival rates of 40%-78%.[6,18] The prognosis of early-stage CCAC is similar to other types of cervical cancer.[8,22] Several large studies reported that both advanced-stage and lymphatic involvement are associated with worse survival.[6,10,18–21] In addition, the presence of positive lymph nodes had a negative impact on RFS (31% vs 92% in patients without lymph node

Table 3 Results of Univariable and Multivariable Cox Regression Analyses of Overall Survival

	Univariable			Multivariable		
	HR	95% CI	P	HR	95% CI	P
Age	0.99	0.96–1.03	0.94			
Lymph node (positive)	2.87	1.14–7.22	0.03	3.05	1.12–8.28	0.03
Tumor size >4 cm	3.31	1.35–8.12	0.01	1.67	0.39–7.17	0.49
Stage of FIGO (IB2-IIA2)	2.49	1.56–3.99	0.02	2.36	1.52–3.68	<0.01
Stromal invasion >2/3	1.95	0.64–5.93	0.24			
LVSI (positive)	1.52	0.55–4.21	0.42			
Vaginal wall extension (positive)	0.05	0.00–2.44	0.74			
Postoperative therapy (yes)	1.73	1.07–2.81	0.03	1.20	0.61–2.35	0.60

Notes: According to clinical significance, the variables included in univariable regression analysis were intermediate risk factors for postoperative diagnosis of the need for further adjuvant therapy. Variables with significant differences (P<0.05) in univariable analysis were included in the multivariable analysis.
Abbreviations: OS, overall survival; FIGO, International Federation of Gynecology and Obstetrics; LVSI, lymphatic vascular space invasion. HR, hazard ratio; CI, confidence interval.

involvement) and OS (80% vs 100%).[18] Long-term follow-up of patients with early-stage CCAC (without intermediate- and high-risk factors) after radical surgery showed no recurrence. Thus, FIGO stage and PLN status were associated with both RFS and OS. Meanwhile, all patients were re-staged with the 2018 FIGO system. The present findings are consistent with the re-emphasis on the classification of lymph node status and surgical staging in the 2018 FIGO guidelines.

The reported overall ovarian metastasis rates ranged from 2.4% to 11.8% in non-squamous cell carcinoma.[23] Of the 47 patients who underwent salpingo-oophorectomy in the present study, two had ovarian metastasis (2/47, 4.26%). Zhou et al[24] reported that ovarian metastasis has no effect on RFS (95% CI: 0.08–4.10, P=0.57) or OS (95% CI: 0.89–9.82, P=0.08). Of more than 100 patients with AC of the cervix (FIGO stage CIS-IIA), none developed an ovarian relapse within a mean follow-up time of 56 months.[24]

Ovarian preservation in young women with early-stage AC of the uterine cervix is safe without the following risk factors: age >45 years, FIGO stage >IB, positive PLNs, deep stromal invasion, LVSI, corpus invasion, parametrial invasion, or tumor size >4 cm.[25] Therefore, young patients, early-stage cases, individuals with a supplementary examination not indicating ovarian abnormalities, and patients with a non-abnormal ovarian appearance perioperatively could consider ovarian preservation suspension surgery.[26] The new 2018 FIGO guidelines are more indicated for early CCAC patients, especially those with fertility requirements who underwent rigorous evaluation before fertility-preserving therapy. In the choice of postoperative adjuvant therapy, chemotherapy (CT) or concurrent chemoradiation (CCRT) does not affect prognosis.[27]

This study has limitations. First, it was a retrospective single-center study with inherent shortcomings. In addition, it had a small sample size because of the rarity of the disease. Therefore, the generalizability of the present findings is limited. Further well-designed studies with large samples are warranted to confirm the current findings.

Conclusion

FIGO stage and lymph node status are independently associated with survival in patients with CCAC without exposure to DES. The choice of postoperative adjuvant therapy needs to be considered comprehensively. Chemotherapy or concurrent chemoradiotherapy has little effect on the prognosis of CCAC.

Data Sharing Statement

No datasets were generated for this study.

Ethics Approval and Informed Consent

This study was approved by the ethics committee of the Obstetrics and Gynecology Hospital of Fudan University (No. 2019-71). The patients had signed informed consents to use medical history and follow-up data, and the study complied with the Declaration of Helsinki.

Consent for Publication

Not applicable.

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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