

Clear-cell carcinoma of the endometrium: type I or type II endometrial carcinoma?

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Summary

Purpose of Investigation: To determine if clear cell carcinoma (CCC) should be classified as a type I or type II carcinoma and provide guidance for clinical treatment. **Material and Methods:** This study included three groups of endometrial carcinomas: 92 cases of CCC were collected from 22 hospitals in China from January 2003 to November 2014, 272 cases of EMA were collected from Peking University People's Hospital from February 2003 and July 2016, and 192 cases of USC were collected from 22 hospitals in China from February 2001 to December 2014. The 2009 FIGO staging system was used and information concerning clinicopathological features was collected. **Results:** The mean age in the CCC and USC groups was higher than that of the EMA group ($p < 0.001$). There was no significant difference in the FIGO Stage between the CCC and EMA groups ($p = 0.158$). There was no significant difference in the extent of myometrial invasion between the three groups ($p = 0.064$), but there was a significant difference in cervical involvement, adnexal metastasis, and lymph node metastasis ($p = 0.017$, $p < 0.001$, and $p < 0.001$). The patients in the CCC, EMA, and USC groups were followed up for an average of 105.6 ± 7.5 months, 135.0 ± 2.2 months, and 92.1 ± 4.4 months, respectively. Fourteen cases with CCC recurred, and 13 ended in death. There was no significant difference between the CCC and the EMA groups in recurrence and death rates ($p = 0.035 > 0.0167$, $p = 0.018 > 0.0167$, $0.0167 = 0.05/3$), but the prognosis in the USC group was worse. **Conclusions:** CCC may follow an overlapping or a third pathway of carcinogenesis, rather than belong to the type II carcinogenesis. Therefore, if CCC should be classified as a type I or type II carcinoma is yet to be determined. Additional studies of the clinicopathological features underlying CCC will facilitate more elective management and avoid unnecessary or non-elective treatments.

Key words: Clear-cell carcinoma; Clinicopathological features; Prognosis.

Introduction

Endometrial carcinoma is the most common gynecological malignant tumor in developed countries, and its incidence is steadily increasing [1]. Traditionally, endometrial carcinoma could be classified into two subtypes, as defined by Bokhman, on the basis of histological characteristics, which differ at the molecular and clinical levels [2]. Type I endometrial cancers are defined as endometrioid and have a relatively favorable prognosis, with the most common subtype being endometrioid adenocarcinoma (EMA). Type II endometrial cancers are non-estrogen-dependent, non-endometrioid, more aggressive, and have a poor prognosis, and the most common subtypes are uterine serous carcinoma (USC) and clear-cell carcinoma (CCC).

The pathology of endometrial CCC was first described in 1911 [3]. It is characterized by the clearing of glycogen and configured in an array of shapes and patterns ranging from solid and glandular to papillary in structure [4]. CCC was considered to have a high rate of recurrence and poor overall prognosis in most published reports [5-8]. However, molecular studies have raised the question of whether CCC should be classified as a type II endometrial carcinoma at

all [9]. Therefore, in this paper, the authors conducted a retrospective study to determine if CCC should be classified as a type I or type II carcinoma and to provide guidance for clinical treatment.

Materials and Methods

This retrospective study included three groups of endometrial carcinomas classified according to histological types, namely, CCC, EMA, and USC. The 101 cases of CCC were collected from 22 hospitals in China from January 2003 to November 2014. Of these, there were nine cases lost to follow up, which were excluded from this study. The authors carried out this study with data from the remaining 92 patients. They also included 272 cases diagnosed as EMA from Peking University People's Hospital in Beijing, China, between February 2003 and July 2016. A total of 192 patients with USC that were treated at 22 hospitals from February 2001 to December 2014 were also included. All histological samples were reviewed and confirmed by pathologists.

Information concerning age, histological findings, disease stage, pathological features, treatment, and follow-up was collected on all subjects. Histological findings, includ-

Table 1. — The comparison of clinical characteristics in CCC, EMA, and USC.

	CCC		EMA		USC		χ^2	p-value
	n	(%)	n	(%)	n	(%)		
Hypertension								
No	72	78.3	172	63.2	146	76	12.282	0.002
Yes	20	21.4	80	36.8	46	24		
Diabetes mellitus								
No	80	87	216	79.4	170	88.5	7.718	0.021
Yes	12	13	56	20.6	22	11.5		
Breast cancer								
No	90	97.8	-	-	186	96.9	0.215	0.643
Yes	2	2.2	-	-	6	3.1		
Nulliparous								
No	87	96.7	-	-	96	52.5	53.353	< 0.001
Yes	3	3.3	-	-	87	47.5		

ing invasion depth, involvement of the uterine cervix and adnexa, lymph node metastasis, and pathological features, including ER, PR, PTEN, and p53, were obtained from the pathology reports. According to the standards of the FIGO system developed in 2009, stage was determined for each case. All patients were treated according to their age, health status, and willingness to develop the corresponding individualized treatment plan. Surgery was the cornerstone of treatment, followed by adjuvant treatments involving radiation therapy, chemotherapy, and hormonal therapy. The adjuvant treatments were determined based on operative findings, histologic features, stage of disease, and any underlying conditions in each patient. These patients were then followed by telephone, correspondence, and outpatient visits. PFS was described as the time between diagnosis and patient recurrence/progression or loss to follow-up. OS was defined as the time between diagnosis and either patient death or loss to follow-up.

Data analysis was conducted using SPSS statistical software (version 24.0). The relationships between various qualitative clinical and pathological parameters were compared using the Pearson chi-squared test or Fisher's exact test. Comparisons of two or more groups of quantitative parameters were performed with Student's *t*-test. Survival curves were plotted using the Kaplan-Meier method, and the log-rank test was used for comparison. Multivariable analysis was conducted using Cox proportional hazards regression. A *p* value of less than 0.05 was considered to represent a significant result.

Results

The age of the patients in this study ranged from 37 to 81 years, with a mean age of 61.5 ± 8.9 years. Hypertension and diabetes mellitus were identified in 20 (21.7%) cases and 12 (13.0%) cases, respectively. Only two (2.2%) cases had a history of breast cancer. Three infertile patients were

Table 2. — The comparison of pathological characteristics in CCC, EMA, and USC.

	CCC		EMA		USC		χ^2	p value
	No	(%)	No	(%)	No	(%)		
FIGO stage								
I	58	65.2	205	75.4	100	52.4	46.705	< 0.001
II	12	13.5	25	9.2	13	6.8		
III	19	21.3	39	14.3	66	34.6		
IV	0	0	3	1.1	12	6.3		
Myometrial invasion								
< 1/2	54	62.1	195	71.7	114	62.3	5.494	0.064
$\geq 1/2$	33	37.9	77	28.3	69	37.7		
Cervical involvement								
Negative	63	68.5	222	81.6	144	81.8	8.169	0.017
Positive	29	31.5	50	18.4	32	18.2		
Adnexal metastasis								
Negative	80	87	264	97.1	138	78	40.749	< 0.001
Positive	12	13	8	2.9	9	22		
Lymph node metastasis								
Negative	55	59.8	242	89	110	59.5	61.883	< 0.001
Positive	37	40.2	30	11	75	40.5		
ER								
Negative	20	47.6	31	11.7	60	42.9	60.195	< 0.001
Positive	22	52.4	233	88.3	80	57.1		
PR								
Negative	29	69	29	11	68	49.3	103.123	< 0.001
Positive	13	31	235	89	70	50.7		
PTEN								
Negative	5	0.5	55	41	-	-	0.303	0.582
Positive	5	0.5	79	59	-	-		
P53								
Negative	3	21.4	107	51	19	14.2	49.341	< 0.001
Positive	11	78.6	103	49	115	85.8		

identified, and there were two cases of unknown maternal history.

Among the 92 cases included in this study, the number with pure CCC was 47.8% (44/92), with the remaining 48 cases showing a mixed histology. Moreover, 39.1% (36/92) of all the patients had a minor amount of EMA, 9.8% (9/92) had a minor amount of USC, and 3.3% (3/92) consisted of CCC, EMA, and USC combined.

Fifty-eight cases (65.2%) were diagnosed at Stage 1, 12 cases (13.5%) at Stage 2, and 19 cases (21.3%) at Stage 3, and no cases were identified at Stage 4. Three (3.4%) cases had no myometrial invasion, 51 (58.6%) cases had superficial myometrial invasion ($< 1/2$), and deep myometrial invasion ($\geq 1/2$) was identified in 33 (37.9%) cases. Cervical involvement was identified in 29 (31.5%) cases. Twelve (13.0%) cases had adnexal metastasis, and 37 (40.2%) cases had lymph node metastasis. In the CCC group, 42 cases expressed ER and PR. ER expression was absent in 20 (47.6%) cases with only focal expression in 22 (52.4%) cases. PR expression was absent in 29 (69.0%) cases, with

Table 3. — The comparison of treatments and survival outcome in CCC, EMA, and USC.

	CCC		EMA		USC		χ^2	p value
	No	(%)	No	(%)	No	(%)		
Chemotherapy								
No	31	34.4	135	49.6	39	20.9	39.606	< 0.001
Yes	59	65.6	137	50.4	148	79.1		
Radiotherapy								
No	77	88.5	211	77.6	113	74.8	6.524	0.038
Yes	10	11.5	61	22.4	38	25.2		
Relapses								
No	78	84.8	251	92.3	128	66.7	50.955	< 0.001
Yes	14	15.2	21	7.7	64	33.3		
Deaths								
No	79	85.9	255	93.7	150	78.1	24.512	< 0.001
Yes	13	14.1	17	6.3	42	21.9		

only focal expression in 13 (31.0%) cases. Loss of PTEN was seen in five (50%) of the ten cases. The expression of p53 was seen in 11 (78.6%) of 14 cases.

All patients were treated with surgery. Of the 92 surgeries, eight were performed laparoscopically and 84 were performed via laparotomy. In 90 cases, the operation included a total hysterectomy and bilateral salpingo-oophorectomy with or without lymph node sampling. The other two cases had a hysterectomy only. Moreover, 59 of 90 (65.6%) cases received adjuvant chemotherapy. Pelvic irradiation was given as part of the primary treatment in ten of 87 cases, with 14 cases experiencing recurrence, and 13 cases resulting in death from tumor. There was no significant difference in DFS between the pure CCC and the mixed CCC groups ($p = 0.714$). The disease-free survival curve is shown in Figure 1.

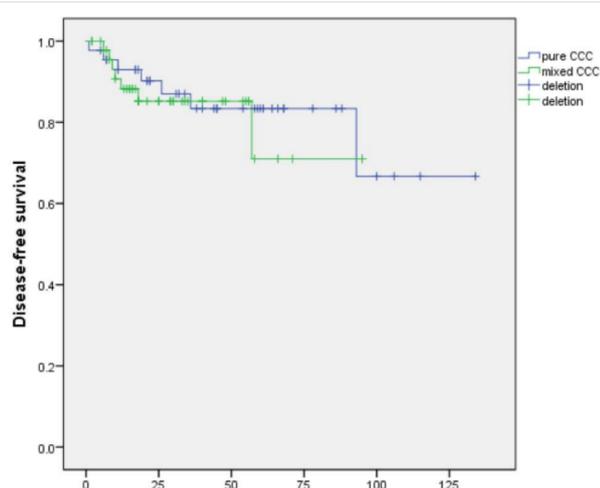


Figure 1. — Disease-free survival of the subtypes of CCC. There is no significant difference in DFS between the pure CCC and the mixed CCC groups ($p = 0.714$).

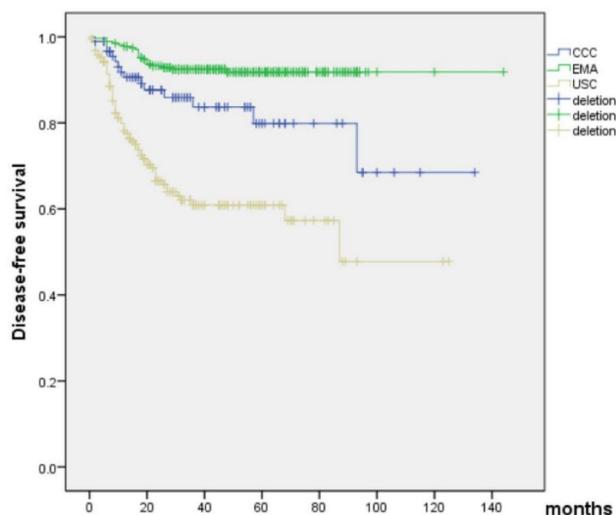


Figure 2. — Disease-free survival in the CCC, the EMA and the USC groups. There is no significant difference between the CCC and the EMA groups in recurrence rates ($p = 0.035 > 0.0167$, $0.0167 = 0.05/3$).

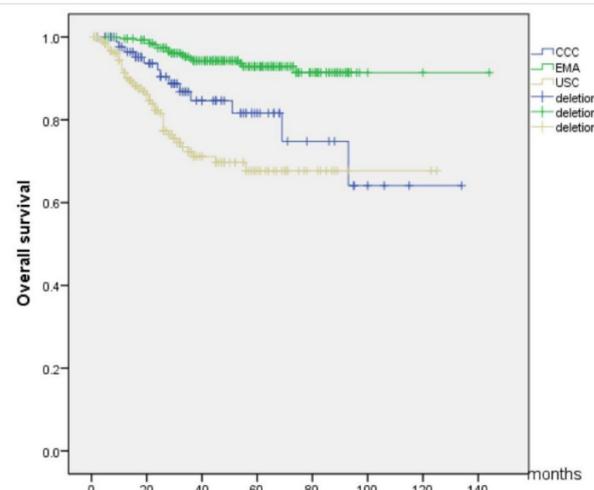


Figure 3. — Overall survival in the CCC, the EMA, and the USC groups. There is no significant difference between the CCC and the EMA groups in death rates ($p = 0.018 > 0.0167$, $0.0167 = 0.05/3$).

The mean age of cases in the CCC, EMA, and USC groups was 61.5 ± 8.9 years, 54.8 ± 8.9 years, and 60.2 ± 7.9 years, respectively. The mean age in the CCC group and the USC group was higher than that of the EMA group ($p < 0.001$). With regards to age and medical disorders such as hypertension, diabetes mellitus, and breast cancer, there was no significant difference between the CCC and the USC groups ($p = 0.596$, $p = 0.679$, $p = 0.700$, and $p = 0.63$, respectively). The other clinical characteristics are shown in Table 1.

Regarding FIGO Stage, there was no significant difference between the CCC and the EMA groups ($p = 0.158$). However, the FIGO Stage in the USC group is advanced when compared to the CCC group, showing a significant difference ($p = 0.003$). There is no significant difference in myometrial invasion between the three groups ($p = 0.064$). There was a significant difference in cervical involvement, adnexal metastasis and lymph node metastasis between the CCC and the EMA groups ($p = 0.008$, $p < 0.001$, and $p < 0.001$, respectively). However, adnexal metastasis and lymph node metastasis in the CCC group were comparable to the USC group ($p = 0.074$, $p = 0.959$, respectively). The comparison of other pathological characteristics between the three groups is shown in Table 2.

In the CCC group, 22 (52.4%) of 42 cases were ER positive, 13 (31.0%) of 42 cases were PR positive, and 11 of 14 cases were p53 positive. There was no significant difference in the rate of ER, PR, and p53 positivity ($p = 0.586 > 0.0167$, $0.024 > 0.0167$, and $0.489 > 0.0167$, respectively, $0.0167 = 0.05/3$) between the CCC and the USC groups. There was no significant difference in the rate of expression of PTEN and p53 between the CCC and the EMA groups ($p = 0.582$ and $p = 0.032 > 0.0167$, respectively, $0.0167 = 0.05/3$).

In the CCC group, the proportion of cases receiving chemotherapy is slightly higher than that of the EMA group ($p = 0.012$), but there was no significant difference in the proportion receiving radiotherapy ($p = 0.026 > 0.0167$, $0.0167 = 0.05/3$). The proportion of cases receiving chemotherapy and radiotherapy in the USC group was significantly higher than that of the CCC group ($p = 0.015$ and $p = 0.011$, respectively). In the USC group, the proportion of cases receiving chemotherapy was higher than that of the EMA group ($p < 0.001$), but there was no significant difference in the proportion of cases receiving radiotherapy ($p = 0.524$).

In the CCC group, 14 (15.2%) of 92 cases relapsed, and 13 (14.1%) cases died of this disease. There was no significant difference between the CCC and the EMA groups in recurrence rates and death rates ($p = 0.035 > 0.0167$ and $p = 0.018 > 0.0167$, $0.0167 = 0.05/3$). However, there was a significant difference between the CCC and USC groups in recurrence rates ($p < 0.001$). The death rates between the CCC and USC groups were comparable ($p = 0.122$). The comparison of treatments and survival outcomes in the CCC, EMA, and USC groups is shown in Table 3.

The patients in the CCC, EMA, and USC groups were followed up for an average of 105.6 ± 7.5 months, 135.0 ± 2.2 months, and 92.1 ± 4.4 months, respectively. The five-year DFS rates in the CCC, EMA, and USC groups were 79.9%, 91.8%, and 60.9%, respectively. The five-year OS rates in the CCC, EMA, and USC groups were 81.6%, 92.9%, and 67.7%, respectively. The disease-free survival and overall survival curves are shown in Figures 2 and 3.

Discussion

CCC has a Müllerian origin [10] with a reported frequency of approximately 5% of all endometrial adenocarcinomas [11, 12]. It is relatively rare and will require additional studies exploring patient characteristics and clinical outcomes. Traditionally, CCC is considered an aggressive subtype of endometrial cancer with a worse prognosis compared to type I cancer [2] and more frequent relapses at distant and extra-pelvic sites. However, recent molecular research has raised doubts as to whether CCC should be classified as a type II endometrial carcinoma [9].

Age at the time of diagnosis is often the most important single factor in determining the prognosis of a patient with endometrial carcinoma [13]. Abeler *et al.* reported that the mean age of patients with CCC was 66.2 years, which was older than patients with EMA [6]. In other studies, the median age was 65 (range 33–83) years [9]. The data from the current study are consistent with the general literature, but the patients in the CCC group were found to be slightly younger, with a mean age of 61.5 ± 8.9 years. For the EMA and USC groups, the mean age was 54.8 ± 8.9 years and 60.2 ± 7.9 years, respectively. There was a significant difference between the three groups ($p < 0.001$) with the mean age in the CCC and USC groups higher than that of the EMA group. It can also be seen from Table 1 that the incidence of hypertension and diabetes mellitus in the CCC and USC groups was significantly lower than that of the EMA group. As another report suggest [14] and this result indicates, unlike EMA, the occurrence of CCC may not be associated with metabolic syndrome, obesity, diabetes or exogenous estrogen exposure. It is also evident that hypertension and diabetes mellitus are not associated with the development of non-endometrioid types of disease [15].

Some studies have suggested that an advanced stage was significantly associated with an increased risk of recurrence [16, 17]. In the present research, there was no significant difference in the FIGO Stage between CCC and EMA ($p = 0.158$). However, the stage in the USC group is advanced compared to the CCC group ($p = 0.003$). Therefore, clearcell carcinoma of the endometrium is comparable to endometrioid adenocarcinoma, in that it is more likely to be detected at an early stage. In the uterine serous carcinoma group, the failure to detect at an early stage is at least partly responsible for the poor prognosis.

It is reported that in the CCC group, estrogen and progesterone were rarely expressed, and diffuse p53 expression, which is associated with TP53 mutation, was only observed in 25% of the cases [18]. A recent study suggests that positive expression of PR correlates with low tumor grade, low recurrence rate, and a higher survival rate [19]. In the present study, CCC had USC-like features such as the rare expression of ER/PR (52.4%/31.0%), intermediate features regarding expression of p53 (78.6%), and EMA-like features regarding losses of PTEN (50%). The immunohistochemical and molecular characteristics in the present

study confirm these similarities that were also noted other reports [20, 21]. A Recent study also indicated that the classification of CCC as being generally ‘high-grade’ or ‘type II’ tumors may not be warranted [9].

In the present literature review, most published reports found that clear-cell tumors are associated with a high rate of recurrence and poor overall outcome [3, 6, 22]. In present study, however, DFS and OS of CCC were found to be comparable to that of the adenocarcinoma. Although the proportion of cases receiving chemotherapy and radiotherapy in the USC group is significantly higher than that of the CCC group ($p = 0.015$ and $p = 0.011$, respectively), the prognosis of USC is worse. Similar to the present result, one study suggests a favorable outcome in clear-cell tumors and no differences were noted between CCC and adenocarcinoma with regard to variables such as age, stage at presentation or response to treatment [23]. Bae *et al.* found no patients with pure CCC that experienced recurrence or died of the disease (0/16, 0%), suggesting that pure CCC should not be regarded as type II carcinoma [20]. Surprisingly, the present authors did not find a higher recurrence rate in mixed-histology patients. In the present study, patients with pure CCC fared as well as those with mixed-histology. The disease-free survival curve is shown in Figure 3. Consistent with the present result, Murphy *et al.* reached the same conclusion [24].

Conclusion

In the present study, it is suggested that CCC may follow an overlapping or a third pathway of carcinogenesis, rather than belonging to type II carcinogenesis. Therefore, if CCC should be classified as a type I or type II carcinoma is yet to be determined. Additional studies of the clinicopathological features underlying CCC will facilitate more elective management and avoid unnecessary or non-elective treatments.

Ethics approval and consent to participate

The manuscript was obtained with the informed consent of all participants. The institutional review board of the Peking University People’s Hospital approved this retrospective study, code 2016PH054-01.

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Conflict of interest

There are no conflicts of interest to declare for any of the authors.

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