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Original article

Prognostic factors in clear cell carcinoma of endometrium: analysis of 55 cases

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Abstract. *Background and aim of the work*: The purpose of this study was to evaluate the clinical and pathologic prognostic factors associated with survival in patients with clear cell carcinoma (CCC) of the endometrium. *Methods:* A retrospective review of fifty-five patients with endometrial clear cell carcinoma were collected. *Results*: The median overall and disease-free survivals were 40 and 20 months, respectively. A univariate analysis was performed with respect to stage of disease, age, lymph nodes status, myometrium invasion, lymph vascular space invasion and adjuvant therapy. Stage was found to be the only important prognostic factor related to survival. In fact, early stage had a median survival of 77 months compared to 34 months in the advanced disease ($p<0.04$). These differences remained significant after adjusting for single stage (stage III versus IV). *Conclusions*: Endometrial CCC is a rare histotype. Advanced stage disease is considered a poor prognostic factor. Recurrences are high even in early stage. Randomized clinical trials are needed. (www.actabiomedica.it)

Key words: prognostic factors, clear cell carcinoma of endometrium, endometrial cancer; stage, survival, recurrence.

Introduction

Endometrial cancer (EC) accounts for 5% of women malignancies worldwide, with a mortality of 2%. It represents the sixth most common cancer among women and the 14th cause of cancer-related death in the world (1).

EC is typically subdivided in type I and type II tumors, according Bokhman classification (2). Distinction is based on different pathogenesis: type I is estrogen related and is the most common type with more than 80% of cases; type II, not estrogen-related, consists of serous carcinoma, clear cell carcinoma and carcinosarcoma.

However, based on molecular pathways many recent studies have subdivided EC in four subtypes with different relation to prognosis (POLE ultramutated, MSI hypermutated, Copy number low, copy number high) (3).

Clear cell carcinoma (CCC) of the endometrium is a rare tumor that comprises 2-4% of endometrial cancers. Despite the endometrioid histotype where the precursor is identified in complex hyperplasia with atypia (3, 4), little is known about CCC precursor, taken into account the absence of relation with hyperestrogenic state. Some authors have supposed the presence of glandular atypia in the endometrium adjacent to CCC, with similar patterns (cytoplasmic clarity and/or eosinophilia with varying degrees of nuclear atypia) (5). Due to its rarity and aggressivity, CCC continues to represent an important challenge. Different series have tried to shed light on prognostic factors concerning CCC. Older age, advanced stage, presence of lymph node metastases, distant sites

metastases, recurrence, have been predictive of poor prognosis (6-8). In our study we analyzed clinical and pathologic factors of CCC in order to evaluate their prognostic role.

Materials and Methods

Between 1995 and 2018, all consecutive cases of endometrial CCC from two academic institutions were collected in order to evaluate clinico-pathologic prognostic factors and the impact of them on the survival.

Mixed histotypes and endometrioid carcinomas with clear cell aspects were excluded. All patients underwent surgery, mostly total hysterectomy (type A according Querleu-Morrow classification) with adnexectomy and eventually association of lymphadenectomy and omentectomy.

The International Federation of Gynecology and Obstetrics (FIGO 2009) staging system was used for the classification of disease. Early stage was defined as stages I-II and advanced stage as stages III-IV.

Regarding adjuvant therapy, a chemotherapy regimen based on carboplatin plus paclitaxel was mostly performed for six or eight cycles. Data were obtained from hospital charts, office records, and tumor registry databases which included: age at diagnosis, stage, lymphadenectomy, adjuvant therapy, depth of myometrial invasion (MI), cervix involvement, adnexal involvement, lymphovascular invasion (LVI), presence of lymph nodes, recurrence and survival outcome. Progression-free survival (PFS) was established from the date of diagnosis until the date of recurrence, whereas overall survival (OS) from the date of diagnosis to the date of death or last follow up. Survival curves for PFS and OS were estimated by Kaplan-Meier method and their differences were evaluated by the log-rank tests. All tests with p values less than 0.05 were considered significant.

Although molecular prognostic factors will play a key role in the management of patients with endometrial cancer in the next future, the assessment of the latter features was out of the aim of this retrospective study, as molecular signatures were not recorded in the analysed dataset.

Results

All data regarding clinicopathological features are reported in Table 1.

Fifty-five cases of endometrial CCC were identified. The median age was 68 (range 19-89). Myometrial invasion < 50% (M1) was found in 28, myometrial invasion >50% (M2) in 21, absence of myometral invasion (M0) in six cases. Lymphovascular space invasion was noted in 32 cases (58%). Adnexal involvement was shown in 9 patients (16%). Twenty-one patients (38%) underwent a systematic pelvic lymphadenectomy whereas four cases (8%) women has a lymph node sampling. Lymph node resulted metastatic in 10 cases (40%). Twenty-three patients had stage I, six stage II, 15 stage III, 11 stage IV disease. All patients underwent primary surgery. In particular, 48 had type A and seven had type B hysterectomy. Fifty-one patients (93%) had a bilateral adnexectomy, while only four underwent a monolateral adnexectomy due to previous contralateral salpingo-oophorectomy. Infracolic omentectomy was performed in 23 patients (42%), whereas in three cases it was a partial procedure.

Thirty patients underwent adjuvant chemotherapy which was for all of them based on carboplatin plus paclitaxel regimen. Adjuvant radiotherapy was performed in five women, whereas chemotherapy followed by radiotherapy in seven patients. Twenty of the fifty-five patients had a recurrence (36%). The majority (60%) of the recurrences were in the pelvis; however six women had distant metastases, primarily in the lung (five cases) and one in the liver. The remaining two patients had both local and distant recurrences. Patients who recurred had stage I in six, stage II in three, stage III in four and stage IV in seven cases (Table 2).

All recurred patients received either chemotherapy or radiotherapy based if the recurrence was local or distant. The median overall survival of the recurred patients from the recurrence to the death or last follow up was 15 months. The median overall (OS) and disease-free survivals (PFS) were 40 and 20 months, respectively (Fig. 1-2).

A univariate analysis was performed with respect to stage of disease (early versus advanced stage disease). Stage was found to be an important prognostic factor related to survival (Fig. 3).

Table 1. Clinicopathological features.

Clinicopathological features	N (%)
Median age (range)	68 (19-89)
Myometrium invasion	
M0	6 (11)
M1	21 (38)
M2	28 (51)
Lymph vascular space invasion (LSVI)	
LVI +	32 (58)
LVI -	23 (42)
Adnexal invasion	9 (16)
Lymphadenectomy	
Not performed	30 (54)
Sampling	4 (8)
Systematic	21 (38)
Lymph Node status	
Positive	10 (40)
Negative	15 (60)
Stage	
I	23 (42)
II	6 (10)
III	15 (27)
IV	11 (20)
Hysterectomy	
Type A	48 (87)
Type B	7 (13)
Adnexectomy	
Bilateral	51 (93)
Monolateral	4 (7)
Omentectomy	
Infracolic	23 (42)
biopsy	3 (5)
Not performed	29 (53)
Adjuvant therapy	
Not performed	13 (24)
Radiotherapy	5 (9)
Chemotherapy	30 (54)
Chemotherapy+radiotherapy	7 (13)
Recurrence	20 (36)
Local	12(60)
Local and distant metastases	2 (10)
Distant metastases	6 (30)

Table 2. Number of recurrences based on stage.

Stage	N recurrences (%)
I	6 (30)
II	3 (15)
III	4 (20)
IV	7 (35)

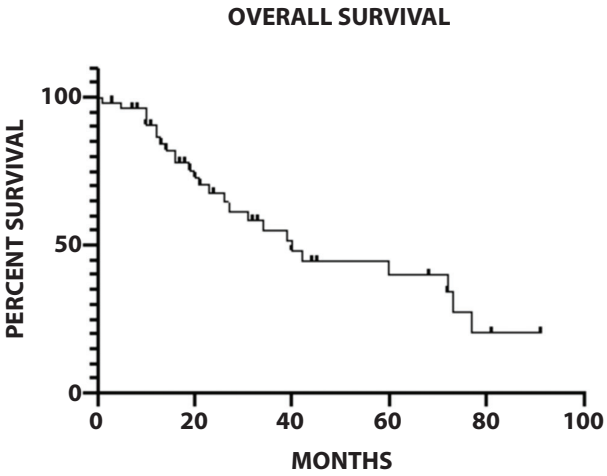

Figure 1. Overall survival (OS).

In fact, early stage had a median survival of 77 months compared to 34 months in the advanced disease ($p<0.04$). These differences remained significant after adjusting for single stage (stage III versus IV). However, no differences in survival was observed between stage I and II.

A univariate analysis was also performed with respect to age (< 65 versus > 65 years old), lymph nodes status (positive versus negative) myometrium invasion (M0 versus M1 versus M2 and M1 versus M2), lymph vascular space invasion (LSVI versus no LVSI) and adjuvant therapy (chemotherapy versus radiotherapy versus chemotherapy followed by radiotherapy and adjuvant therapy versus no adjuvant therapy). However, these variables were not found to be important prognostic factors related to survival.

Discussion

CCC of endometrium is a rare tumor that comprises 2-4% of endometrial cancers (6). Its rarity explains the lack of data in the literature that comes from retrospective analyses in many cases. Moreover, the absence of a standardized therapeutic plan adds more complexity to this aim. Many studies found an older age at diagnosis compared to type I endometrial cancers. In our series a median age of 68 years (range 19-89) was observed, thus setting 10 years later the age

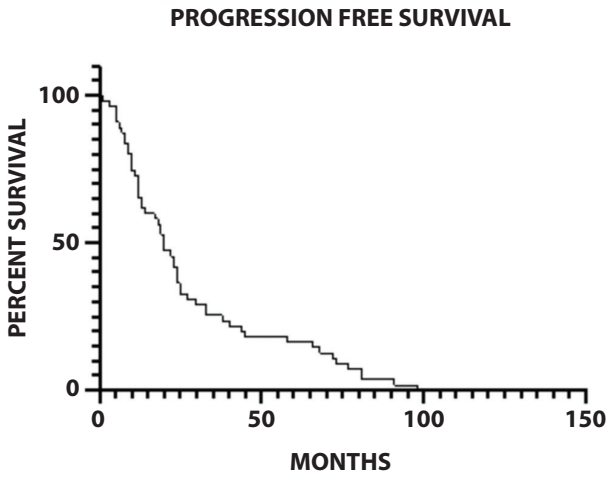

Figure 2. Progression free survival (PFS).

of diagnosis compared to type I endometrial cancers consistent with other studies (6, 7). Most patients are in menopausal age, without typical risk factors identified for type I cancers (9). Vance et al suggested that older age at CCC diagnosis seems to be related with a worse outcome (10). However, this was not confirmed from our data.

A common feature noticed in CCC is the myometrial involvement. In our study it is close to 80% and it is similar to that reported from many series (9). Nevertheless, Abeler et al (8) and also confirmed by Abdulfatah et al (6), founded that myometrial invasion is an important prognostic factor in addition to advanced stage disease, older age at diagnosis and adnexial involvement. In our series, we were not able to demonstrate a worse outcome associated to myometrial invasion.

On the other hand, regarding LSVI, Abeler et al (8) showed to be a prognostic factor, however other studies, including ours, were not able to prove (6, 11, 12). Despite that, LVSI remains a typical feature of CCC presenting in 58% of patients that is similar to data found in the literature (6, 8).

For what concerns the treatment, surgery represents the gold standard. Total abdominal hysterectomy, with bilateral adnexectomy associated with systematic lymphadenectomy should be performed for surgical staging. Sari et al (13) pointed out the importance of omentectomy for a correct staging, due to the fact that extrauterine involvement may also result in absence of myometrial invasion and the omentus is proven to

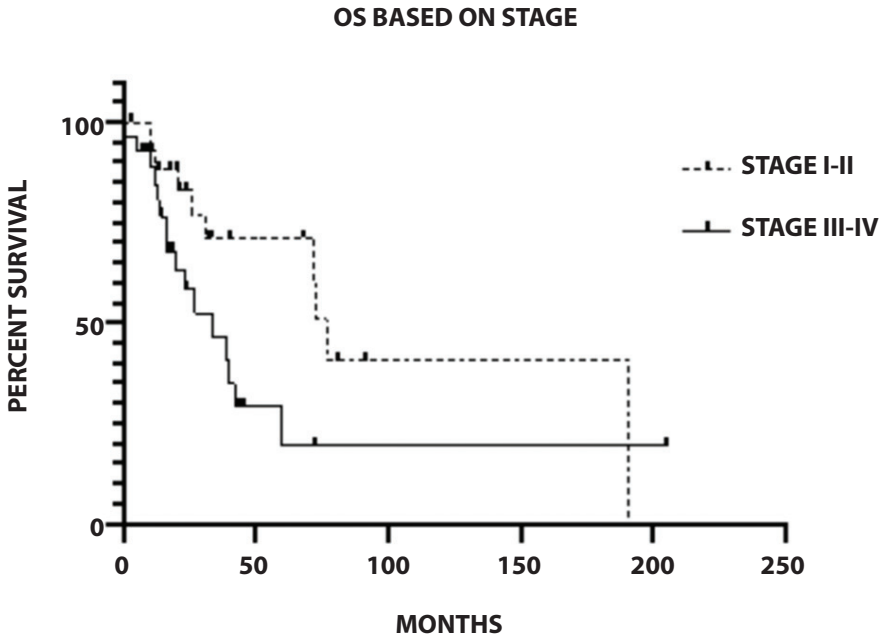

Figure 3. OS based on stage (stage I-II versus III-IV, p=0.04).

be the most common metastatic site. In our patients omentectomy was performed for about half cases, but it was not considered a standard procedure.

Regarding lymphadenectomy, Mahdi et al (14) evaluated 1385 patients of endometrial CCC; of these, 955 (69%) underwent this procedure. In this study OS was found to be increased of 32% and 47% when 1 to 10 lymph nodes or more than 10 lymph nodes were removed, respectively, compared to those who did not undergo lymphadenectomy. A systematic lymphadenectomy leads to a better outcome in many studies (15, 16). In contrast with these results, the study by Hamilton et al (7), which compared serous-papillary carcinoma and CCC with endometrioid G3 carcinoma, did not find a significative impact of lymphadenectomy on survival. In our series, lymphadenectomy both systematic or sampling was performed in 46% of the patients. Of these, positive LN status was demonstrated in 40% of cases. Similarly to data from Hamilton et al, lymphadenectomy showed no prognostic value.

We found stage to be a prognostic factor; in particular advanced stages are related with a worsening of survival (median of 34 months in advance compared to 77 months in early stages). A prognostic difference was also found comparing advanced stages (III versus IV), but not comparing early stage (I versus II). Importance of staging as an indipendent prognostic factor is widely demonstrated in literature (17, 18).

Adjuvant therapy for CCC does not lead for a standardized protocol and literature is conflicting in this regard. A Society of Gynecologic Oncology review suggests a platinum based adjuvant chemotherapy (19). Some studies (20, 21) evaluated that adjuvant chemotherapy is not necessary in stage I disease. Radiotherapy provides better efficiency when performed in early stages disease, (22); on the contrary, its action is reduced in case of extrauterine spread of the disease. Nevertheless, improvement of OS is not achieved when radiotherapy is carried out (19).

In our study, chemotherapy with or without radiotherapy was performed in about 67% of cases and it was mostly based on platinum regimen associated with paclitaxel (80%). Radiotherapy alone (EBRT or BT) was carried out in 9% of cases. No differences in median overall survival were found among the three treatment groups and between who received adjuvant treatment and who do not receive. From our study, the role of adjuvant therapy and which subset of patients could better take advantage of it is still controversial.

CCC has a peculiar tendency to distant recurrence even in early stages. Abeler et al (8) showed that two-thirds of the recurred patients, relapsed outside the pelvis. This has been confirmed in the study published by Murhphy's et al (23) where the authors showed 24% of distant recurrences. In addition, many studies showed that the most site of distant recurrences are liver, bones, lymph nodes (in particular para-aortic nodes) and lung (9, 11, 23). Similarly to that reported by Foerster et al (22), we found that lung is the most involved site of distant relapse. In fact, five of the six patients who had a distant recurrence developed a lung metastases. According with the literature, recurrencies are very common and from our data it has been showed that a 36% of the patients population recurred (6, 23 24).

We found that the median PFS was of 20 months which is lower that typically observed from other studies that varying from 38 to 64 months (6-11). It could be explained that it is a small simple size of patient's and this is related to the rarity of the disease.

Surgical treatment remains the gold standard even if uncertain is the role of a systematic lymphadenecomy in the outcome improvement (25). Controversial is the prognostic relevance of myometrial invasion and LVI, despite being very common features in CCC. A negative prognostic factor is given by stage disease, with an evident decrease of OS between early stage and advanced stage and also between stage III and IV. No differences in survival were observed in early stage between stage I and II. Adjuvant treatment either chemotherapy and radiotherapy does not seem to impact the outcome. The number of relapses remains elevated with a predilection for distant sites.

In conclusion, clear cell carcinoma represents a rare histotype, affecting elderly patients, without being associated to type I endometrium carcinoma risk factors. For this reason we believe that our series of patients coming from data of two academic Institutions could be an useful addition to the current literature. However, new trials from biomolecular analyses are needed in order to better focalize more accurate treatment indications.

Conflicts of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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