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Research Article

UTERINE CLEAR CELL CARCINOMA: CLINICAL AND PATHOLOGICAL FEATURES

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ABSTRACT

Uterine clear cell carcinoma (CCC) is an aggressive histologic subtype of endometrial cancer EC associated with a higher risk of recurrence and death. Retrospective review including 64 patients with CCC diagnosed between 2001 and 2014 at 3 institutions was conducted to evaluate clinicopathologic parameters and clinical behavior of this subtype of EC.

INTRODUCTION

Endometrial cancer (EC) is the most common gynecological malignancy in developed countries. Most endometrial cancers are endometrioid adenocarcinoma and only approximately 3-5% are uterine clear cell carcinomas (CCC) (1). It is an aggressive histologic subtype associated with a higher risk of recurrence and death related to uterine cancer (2). The aim of this study was to analyze pathologic features and evaluate the clinical behavior of CCC.

MATERIAL AND METHODS

We conducted a multicentre retrospective study between 2001 and 2014 at three tertiary medical centers in Spain ("Hospital Clinico San Carlos" in Madrid, "Hospital Virgen del Rocio" in Seville and "Hospital Universitario Miguel Servet" in Zaragoza). A total of 64 women with CCC were included. Histotype was reviewed by at least two local gynecological pathologists using current World Health Organization criteria. Others subtypes of EC were excludedHysterectomy with bilateral salpingo-oophorectomy, staging biopsies, omentectomy, and cytoreductive procedures were carried out in all patients. Pelvic lymph node dissection associated or not with para-aortic lymphadenectomy (LDN) was performed in 43 patients (67,2%). The reasons for not performing the lymphadenectomy included morbid obesity, advanced age, presence of comorbidities, and presurgical tumor classification as no high-grade EC. All of them were evaluated at Local Tumor Committees integrated by radiation oncologists, clinical oncologists, pathologists and gynecological oncologists. Follow-up was performed according to National practice and guidelines.

Continuous variables were expressed as means and standard deviations (SD) and interquartile ranges (IQR). Kaplan-Meier's method was used to estimate the overall survival (OS) and disease-free survival (DFS) across the study. For statistical analysis, the data obtained were transcribed into a computerized database using the Statistics Process Social Sciences 22.0 package. The study was approved by the Institutional Review Board of each participant Center.

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RESULTS

Demographic data and risk factors are shown in Table 1. The median age of all patients was 71.9 years. Almost all of the patients were postmenopausal, about 55% were hypertensive and 39.7% were obese. Almost 25% of all the patients had a family history of cancer (the majority breast and colon), 12.7% had a personal history of cancer (the majority breast and colon) and 6.2% were being treated with tamoxifen.

The most common presenting symptom for patients was abnormalbleeding (90.5%). Histo-pathological data at diagnosis are shown in Table 2. Most of the patients had deep myometrial invasion (59.4%) and 39.1% lymphovascular space involvement. Istmo affectation was informed in 37.5% and positive peritoneal whasings in 12.7%. There were nodal involvement in 41.8% of the patients, of which, 39% were pelvic and 28.5% were paraaortic. Most of the patients, 59.4%, were diagnosed in early stage (I/II) and 40.6% in advanced stage (III/IV). Adjuvant treatment, radiotherapy, chemotherapy or both, was administered in 70.3% of the patients. The others, did not receive any treatment due to complications of surgery, advanced age, co-morbidities, or refusal.

Table 1 Demographic and risk factors details of 64 patients with CCC. Data are shown as mean (standard deviation) or cases (%).

	CCC (n=64)
Age (years)	71.9(10.1)
History of cancer in family	15(23.8)
Personal history of cancer	8(12.7)
Menopause	
Postmenopausal	61(95.3)
Premenopausal	3(4.7)
Hypertension	35(54.7)
Diabetes	20(31.3)
Obesity (IMB>30)	26(39.7)
Nuliparity	9(14.3)
Hormonal treatment	1(1.6)
Tamoxifene treatment	4(6.2)

Table 2 Histological, surgical and adjuvant features in 64 patients with CCC. Data are shown as cases (%)

	CCC (n=64)
Myometrial invasion	
• No invasion	10(15.7)
• <50%	16(25)
• >50%	38(59.4)
Lymphovascular space involvement	25(39.1)
Positive peritoneal washings	8(12.5)
Istmo affectation	24(37.5)
Node involvement (n=43)	18(41.8)
Localization of positive nodes	
• Pelvic (n=41)	16(39)
• Paraaortic (n=21)	6(28.5)
Adjuvant Treatment	
• None	19 (29.7)
• Irradiation	41 (64.1)
• Chemotherapy	15 (23.4)
• Irradiation and Chemotherapy	11 (17.2)
FIGO stage initial/advanced	
• I/II	38(59.4)
• III/IV	26(40.6)

The median follow-up of patients was 31.5 months (IQR 12-65 months). A total of 23 (35.9%) patients experienced a relapse. Distant metastases (60.9%) were significantly more common than pelvic (13%) or nodal recurrence (26.1%). Survival analysis showed a 3-year DFS of 62.8%. During the follow-up 14 patients (21.9%) died, being the 3-year OS rate of 74%.

DISCUSSION

Clear cell endometrial carcinoma was first described in the English literature in 1957 (3). It is an infrequent but aggressive histologic subtype of EC that has distinct clinical and pathologic characteristics and accounts for a high number of recurrences and deaths.

EC has traditionally been subdivided into two dichotomous categories, Type I and II, based on clinical and histologic differences (4-6). Type I EC typically arises in a setting of a hyperestrogenic milieu from unopposed estrogenic states such as obesity. They trend to be well differentiated, endometrioid histology, diagnosed at early stages, and associated with good prognoses. Type II EC have classically been presumed to be estrogen independent, poorly differentiated, frequently in advanced stage, and associated with worse prognosis. Most consist of uterine serous carcinoma or CCC histologies. Recent studies have suggested that these traditional distinctions between Type I and II EC may be inaccurate and some risk factors such as obesity, hypertension and diabetes may be shared by both (7-9).

Myometrial invasion has been widely studied as a factor of poor prognosis in EC. Deep myometrial invasion has been recognized as a predictor of extra-uterine metastasis and an independent prognostic factor in EC. Mariani *et al* reported that the presence of deep MI was the best predictor of hematogenous dissemination in corpus cancer (10). In our study, it was a highly frequent factor in CCC, 59,4% of the patients, however in other studies such as Ayeni et el (11), the percentage of deep myometrial invasion reported was lower, 22.5% of the patients.LVSI is considered one of the first steps of metastatic spread in EC, and it is an important prognosis factor of recurrence and survival. In our study it was a high rate of LVSI in the hysterectomy specimen (39.1%). In the last European consensus conference on endometrial cancer, LVSI was agreed to be an important risk factor that can be employed to define new risk groups and guide adjuvant therapy use.(12). The high association of both pathological factors could explain the diagnosis in advanced stage of CCC.

Because of its aggressive behavior and high rate of occult extrauterine spread, comprehensive surgical staging including lymphadenectomy is recommended for patients with CCC. Women presumed to have early stage UCCC are often upstaged at the time of surgical staging. Thomas *et al* (13) found that 20% of patients with disease clinically confined to the uterus had positive lymph nodes. This is confirmed by the high rates of nodal involvement found in our study. There is no conclusive evidence demonstrating that lymphadenectomy has a positive impact on survival in EC. In a critical review of literature, the rationale for the performance of a lymphadenectomy was that, apart from facilitating disease staging, this procedure seems to offer a measurable survival benefit (14). A study that included 1.385 patients using the population database of the Surveillance, Epidemiology, and End Results (SEER) program investigated the association of lymphadenectomy with survival in women with CCC. The authors concluded that lymphadenectomy was associated with improved survival in CCC (15). However, some studies have

found no evidence that lymphadenectomy provides any survival benefit in high risk EC (16,17).

Most of our patients (77,2%) received adjuvant therapy (radiotherapy or chemotherapy alone or in addition). National and international guidelines contemplate radiotherapy and chemotherapy in high grade EC as part of primary treatment. The adjuvant therapy in high risk EC has been evaluated in two clinical trials which included patients with EC FIGO stage I-III with no residual tumor after the surgery, who were randomly allocated to adjuvant radiotherapy with or without sequential chemotherapy (18,19). In the combined analysis of these trials, the addition of adjuvant chemotherapy to radiation improved DFS (20). Recently a international, randomised, phase 3 trial involving 103 centres in six clinical trials collaborating in the Gynaecological Cancer Intergroup has been published (21). The objective was to investigate the benefit of adjuvant chemotherapy during and after radiotherapy (chemoradiotherapy) versus pelvic radiotherapy alone for women with high-risk endometrial cancer concluding that it did not improve overall survival.

Many studies have suggested the aggressive behavior and poor prognosis of CCC with low rates of DFS and OS (11,13, 22, 23). This subtype of EC has high propensity for extrauterine spread. In the literature, consistent with our study, high dissemination rates are reported at the time of diagnosis (24,25). Furthermore it is related with high recurrence risk, especially in upper abdomen, and distant sites in two thirds patients with recurrence were informed. In concordant with our study, the pelvic relapse is not usually the most common(13).

The potential limitations of this study are its retrospective design, the incomplete staging of some patients (LDN was performed in 67.6%), and the median follow up, which was less than three years. The strengths of the study are the high number of patients and its multicentre design.

No potential conflict of interest relevant to this article wasreported.

CONCLUSIONS

CCC is a rare and aggressive subtype of EC with high association with classical risk factors of EC, pathological factors of poor prognosis and dissemination at diagnosis. Relapses are frequent and often occur outside the pelvis, which is important in the follow-up.

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