

Clear Cell Carcinoma of the Endometrium: A Report of 4 Cases

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Abstract: Clear cell carcinoma (CCC) is a rare but aggressive subtype, accounting for less than 5% of all uterine carcinomas. Several clinicopathological characteristics have been predictive of a poor prognosis; however, the data remain controversial. We report a retrospective study of endometrial CCC diagnosed between 2020 and 2022 at the Hassan 2 University Hospital in Fes, to evaluate clinicopathological parameters: age, tumor size, stage, myometrial invasion (MI), lymphovascular invasion, lymph node and adnexal involvement and adjuvant therapy.

Keywords—Carcinoma, Clear cells, Endometrium, Cancer.

1. INTRODUCTION

Clear cell carcinoma is a rare yet aggressive subtype, representing less than 5% of all uterine carcinomas. Microscopically, CCC is characterized by clear, often eosinophilic, hobnail cells displaying various architectural patterns including solid, papillary, and tubulocystic. Similar histologic features are observed when CCC occurs in the ovary, cervix, and vagina. Unlike endometrioid and serous carcinomas, there is limited data on potential precursor lesions for endometrial CCC. Recent studies have identified a range of atypical glandular changes adjacent to CCC in the endometrium, suggesting they could represent early morphologic features of this tumor. Patients with CCC are typically older, present with higher-stage disease, and have a poorer prognosis compared to those with endometrioid carcinoma. Reported 5-year overall survival rates for advanced-stage (stages III-IV) disease range from 42.3% to 62.5%, indicating the need for more aggressive adjuvant treatment.

2. MATERIALS AND METHODS:

We report a retrospective study of endometrial CCC diagnosed between 2020 and 2022 at the Hassan 2 University Hospital in Fes, to evaluate clinicopathological parameters: age, tumor size, stage, myometrial invasion (MI), lymphovascular invasion, lymph node and adnexal involvement and adjuvant therapy.

3. RESULTS

3.1. CLINICOPATHOLOGIC FEATURES

The median age at diagnosis was 63,75 years (mean, 31 years; range, 50–81 years). The median tumor size at the time of surgical resection was 5,75 cm (4–8 cm). Myometrial invasion extending to the inner half was present in a high proportion of cases (75%), and no invasion was seen in all cases, Lymphovascular invasion was identified in 50%, whereas adnexal involvement 25% of cases. All patients had lymphadenectomy performed as part of surgical staging, No patient presented positive lymph node metastasis, The FIGO stage distribution was 75% stage I, 0% stage II, 25% stage III, and 0% stage IV.

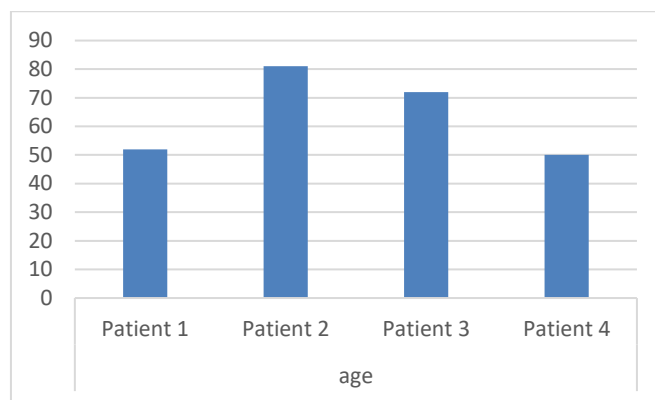


Fig2: graph showing the age of patients

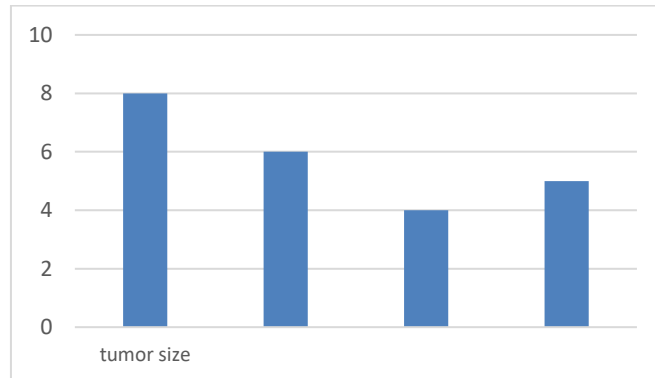


Fig2: graph showing the different tumor sizes

3.2. TREATMENT CHARACTERISTICS

All patients underwent total hysterectomy and bilateral salpingo-oophorectomy. Lymphadenectomy was performed in all patients, whereas omentectomy was performed in only 75% of patients. Radiotherapy, in the form of vaginal brachytherapy and/or whole pelvic radiation therapy, was part of the adjuvant treatment in 50% of patients. Three patients received adjuvant chemotherapy.

4. DISCUSSION

Uterine clear cell carcinoma (CCC) is notably rare, accounting for less than 5% of all endometrial carcinomas (ECs). Unlike its counterparts in the cervix and vagina, there

is no known association with diethylstilbestrol; however, radiation and tamoxifen have been implicated in a subset of cases. ²Patients with CCC are typically post-menopausal and tend to be older, with a median age of 66 to 68 years³, compared to those with endometrioid carcinoma. Despite being classified as a high-grade carcinoma, the disease is primarily confined to the uterus (stages I–II) in most cases. Myometrial invasion is present in approximately 80% of cases, with lymphovascular invasion (LVI) in about 25%⁴. In line with these findings, Abeler et al.⁵ reported a series of 181 patients with CCC, predominantly presenting with early-stage disease, with documented myometrial invasion and lymphovascular invasion in 75% and 37% of cases, respectively. Pathologic stage and patient age were identified as the most significant prognostic factors for CCC based on a study by Hamilton et al.⁶ Their analysis, using SEER (Surveillance, Epidemiology, and End Results) data, compared clinicopathologic prognostic factors and outcomes of patients with serous carcinomas, CCC, and high-grade endometrioid carcinomas (G3EC). Patients diagnosed with serous carcinomas and CCC were notably older (median age 70 years and 68 years, respectively) and had significantly poorer prognoses compared to those with G3EC. Previous reviews have highlighted CCC's tendency for extrauterine disease spread, with relapses more commonly occurring beyond the pelvis⁷. In our series, most patients presented at an older age (median age 63,75 years), with stage I–II disease in 58%, myometrial invasion in 76%, and lymphovascular invasion in 34%. Additionally, advanced stage, older age at diagnosis, presence of deep myometrial invasion, and adnexal involvement were significant predictors of a worse prognosis, consistent with previous literature. In line with our results and previously published data, a recent study by Varughese et al. demonstrated that age and stage significantly impact overall survival (OS), while lymphovascular invasion had no effect on survival in CCC.

Lymphovascular invasion plays a crucial role in tumor metastasis and serves as a significant prognostic factor in EC. Presently, the standard approach for evaluating LVI involves morphological examination of hematoxylin-eosin–stained tissue sections. Stringent morphological criteria for LVI include tumor clusters adhering to the vessel wall, endothelialization of tumor clusters, or the presence of a thrombus connecting tumor clusters to the vessel wall. Alexander-Sefre et al.⁸ investigated the clinical relevance of LVI detected through immunohistochemical staining for vascular endothelial markers in stage I endometrioid EC patients, concluding that immunohistochemically detected LVI seems to lack statistically significant clinical value.

In contrast, Abeler and Kjørstad⁹ observed that LVI and MI serve as robust prognostic indicators in CCC. Additionally, it is well established that patients with CCC face a higher risk of thromboembolic events, particularly in advanced-stage disease; however, the precise mechanism behind this

phenomenon remains unclear¹⁰. Future studies to delve deeper into this hypothesis are recommended, along with consideration of prolonged prophylaxis in these patients to mitigate such occurrences.

5. CONCLUSION

L'insertion vélamenteuse du cordon dans les grossesses gémellaires en général, et plus spécifiquement dans le cas des jumeaux monochoriales bi-amniotiques, est associée au risque de retard de croissance fœtale sélectif et à une discordance significative du poids à la naissance entre les jumeaux. La délimitation échographique de l'insertion placentaire du cordon au premier trimestre pourrait être nécessaire dans l'évaluation précoce du risque de troubles ultérieurs de la croissance fœtale chez les jumeaux. Des études prospectives sont nécessaires pour évaluer la valeur et la précision prédictive de ce potentiel marqueur de dépistage.

Although total abdominal hysterectomy and bilateral salpingo-oophorectomy with comprehensive surgical staging (including peritoneal washing, omentectomy, and pelvic and para-aortic lymphadenectomy) represent the standard first-line therapy for uterine CCC, defining optimal postoperative management remains a challenge. Treatment approaches vary across different stages, and due to the limited number of women affected by uterine CCC, identifying factors associated with improved survival is complex. The Society of Gynecologic Oncology has reported that adjuvant pelvic and/or whole abdominal radiotherapy has not demonstrated benefit in women diagnosed with uterine CCC. For stage III or IV disease (extrauterine involvement) and recurrent disease, they recommend adjuvant chemotherapy with cisplatin, taxol, and doxorubicin, either as doublet or triplet combinations¹¹. Conversely, an observational study involving 80 patients with CCC revealed that vaginal brachytherapy, either alone or in combination with other radiation therapy, significantly improved overall survival (median, 140 vs. 50 months; $P = 0.02$), but did not enhance progression-free survival. Additionally, it was observed that adjuvant chemotherapy alone or combined with vaginal brachytherapy did not significantly impact overall survival or progression-free survival¹².

In a comprehensive examination across multiple institutions regarding surgical interventions and adjuvant treatments for uterine CCC, researchers concluded that vaginal brachytherapy might suffice for stages I and II. This was substantiated by the observation that lymph node dissection and pelvic radiation therapy could offer benefits to patients susceptible to lymph node recurrence¹³. Another study by Smith et al.¹⁴ evaluated 26 patients diagnosed with stages I–IV CCC of the endometrium who underwent postoperative irradiation. The findings revealed that the 3-year disease-free survival and overall survival rates were 47% and 68% for the entire cohort, respectively. For patients with stages I and II disease, these rates increased to 87% for both parameters, whereas for those with stages III and IV disease, the rates were 32% and 61%, respectively. Consequently, adjuvant

radiotherapy proved to be efficacious for patients with early-stage disease, whereas its efficacy was limited for those with advanced-stage tumors, suggesting a potential benefit from clinical trials involving radiotherapy with concurrent or sequential chemotherapy.

6. CONCLUSION

In summary, it was observed that endometrial clear cell carcinoma (CCC) occurred more frequently in older women and was associated with a poorer prognosis, particularly in cases of advanced stage, deep myometrial invasion (MI), adnexal involvement, and older age at diagnosis. The use of adjuvant radiotherapy notably improved the 5-year overall survival (OS), underscoring the importance of considering more aggressive adjuvant treatments. Further investigations at the molecular level may provide deeper insights into the biology of this tumor.

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