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Original Research Article

Clear cell carcinoma of the ovary: clinical profile and treatment outcomes-an experience from tertiary cancer centre in South India

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ABSTRACT

Background: Clear cell carcinoma of the ovary is a rare and aggressive subtype of epithelial ovarian cancer, accounting for approximately 5-10% of all ovarian malignancies. Characterized by unique histopathological features and a high degree of resistance to conventional platinum-based chemotherapy, its management is particularly challenging. This study aims to analyses the clinical profile, treatment modalities, and survival outcomes of 26 patients diagnosed and treated for clear cell carcinoma of the ovary at our institute, with the goal of identifying factors that contribute to improved prognosis and survival.
Methods: We conducted a retrospective cohort study involving 26 patients diagnosed with clear cell carcinoma of the ovary between 2011 and 2020. Data on patient demographics, clinical presentation, treatment regimens, and survival outcomes were extracted from medical records. Statistical analysis included the using Kaplan-Meier survival curves to evaluate overall survival (OS) and progression-free survival (PFS).
Results: The median age of the patients was 52 years, with 42.3% being premenopausal and 57% postmenopausal. Most common presentation were abdomen distension and abdomen pain/discomfort. Median overall survival of clear cell carcinoma was 36 months, and the median disease-free survival was 18 months. Early-stage diagnosis and optimal cytoreduction during surgery were associated with improved survival. Our findings highlight the importance of early detection and aggressive surgical management in improving outcomes for patients with clear cell carcinoma of the ovary.
Conclusions: Clear cell carcinoma ovary relatively uncommon cancer. Patients diagnosed at an early stage demonstrated significantly better OS and PFS compared to those diagnosed at advanced stages. This study finding highlight the aggressive nature of this subtype and the critical importance of early detection and optimal surgical intervention. The study also underscores the challenge of chemo resistance in advanced-stage disease, emphasizing the need for innovative treatment strategies.

Keywords: Clear cell carcinoma, Ovarian cancer, Clinical profile, Treatment outcomes, Survival analysis, Platinum-based chemotherapy, Cytoreductive surgery

INTRODUCTION

Clear cell carcinoma of the ovary is a distinct and aggressive subtype of epithelial ovarian cancer that accounts for 5-10% of all ovarian malignancies. The highest incidence observed in Asian population.[1] Unlike the more common serous type of ovarian cancer, clear cell carcinoma is characterized by cells that appear clear due to the presence of glycogen, and it often exhibits a hobnail cell pattern when viewed under a microscope.[2-5] This subtype tends to be diagnosed at an earlier stage compared to other ovarian cancers, However, despite this early detection, clear cell carcinoma is notorious for its poor prognosis and resistance to conventional platinum-based chemotherapy, which is the standard treatment for ovarian cancer

Patients with clear cell carcinoma often present with symptoms such as abdominal pain, bloating, and ascites. The tumour is frequently associated with endometriosis, suggesting a potential etiological link that distinguishes it from other ovarian cancers.[8,9] Para neoplastic syndromes also part of presenting symptoms. Clinically, clear cell carcinoma is marked by its aggressive behaviour and propensity for early spread to the lymphatic system and distant organs. This aggressive nature, coupled with its chemo resistance, makes treatment particularly challenging. The pathogenesis of clear cell carcinoma remains under investigation, but studies have indicated a significant genetic component, with frequent mutations observed in the ARID1A gene, a key regulator of chromatin remodelling.[11] Standard treatment protocols, which are effective for other subtypes of epithelial ovarian cancer, often fall short for clear cell carcinoma, leading to poorer outcomes. Innovative therapeutic approaches, including targeted therapies and immunotherapy, are currently being explored to improve patient prognosis.

The objective of this study is to evaluate the clinical profile, treatment modalities and survival outcomes of patients with clear cell carcinoma and we aimed to identify factors that significantly influence patient prognosis and overall survival, providing valuable insights that can guide future clinical management and research.

METHODS

This study is a retrospective analysis of 10 years data of clear cell carcinoma ovary patients at our hospital record section, Institute of Obstetrics and Gynaecology, Madras Medical College, Chennai (2011 to 2020). This involves a detailed examination of patient age, menopausal state, parity, presenting symptoms, tumour stage, treatment strategies including surgical interventions (upfront/ interval surgery) and chemotherapy (neo adjuvant/ adjuvant). Follow up protocol every 3 months for first 2 years, every 6 monthly follow up for next 3 years followed by annually. End points of the study were disease free survival (DFS) and overall survival (OS). Disease free survival was defined as time from primary treatment to date of disease progression or recurrence. Overall survival was defined as length of time patient alive from date of diagnosis or treatment started. A survival analysis based on Kaplan-Meier method compared between early and late stage of disease.

RESULTS

Patient demographics and clinical characteristics

This study analysed 26 cases of ovarian clear cell carcinoma from 2011 to 2020. Incidence around 1.73%. The age of patients diagnosed with clear cell carcinoma of the ovary at our institute ranged from 38 to 72 years, with a median age of 52 years (Figure 1). Regarding parity and menstrual status, 19 patients (73%) were uniparous and multiparous (Table 1) and 15 patients (57.69%) were postmenopausal (Table 2). The most common presenting symptoms were abdominal mass/distension and abdominal discomfort/pain (Figure 2). Most of the tumour were unilateral and measured average size of more than 14 cm. CA 125 levels ranged from (26–980 IU/ml). The stage wise distribution highlights the aggressive nature of clear cell carcinoma, often presenting at an advanced stage (Table 3).

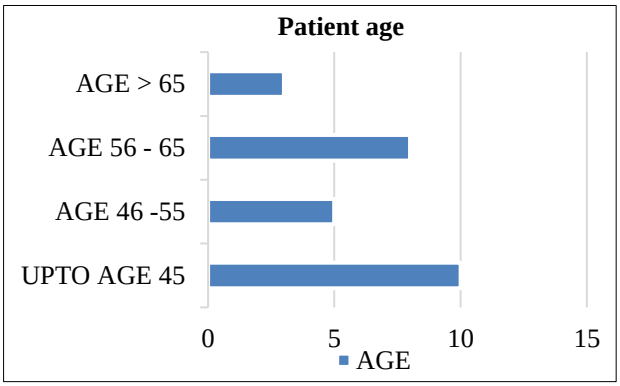

Figure 1: Patient age.

Table 1: Parity status.

Parity status	Number of patients (%)
Nulliparous	7 (26.92)
Uniparous and multiparous	19 (73)

Table 2: Menstrual status.

Menstrual status	Number of patients (%)
Premenopausal	11 (42.30)
Postmenopausal	15 (57.69)

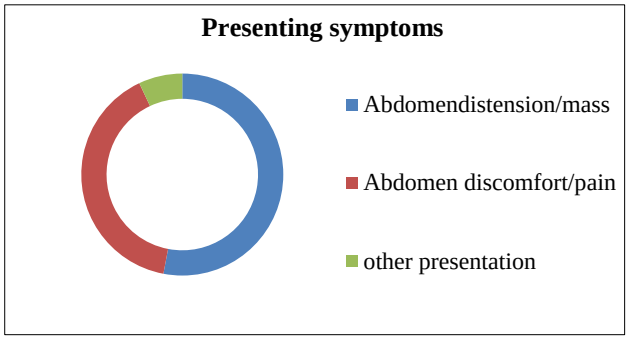

Figure 2: Presenting symptoms.

Table 3: Stage distribution.

Stage	Number of patients (%)
Stage I	7 (26.9)
Stage II	2 (7.6)
Stage III	13 (50)
Stage IV	4 (15.3)

In 26 patients, 19 patients underwent staging laparotomy procedure (total abdominal hysterectomy with bilateral salpingo-oophorectomy, peritoneal washing, omentectomy pelvic lymph node dissection and para-aortic lymph node dissection). Upfront surgery in 9 patients, Interval cytoreduction in 13 patients, complete cytoreduction in 11 patients, sub optimal cytoreduction in 2 patients, 2 patients' surgery deferred due to disease progression during Neo adjuvant chemotherapy and 2 patients presented with liver metastasis so started with palliative chemotherapy.

Chemotherapy delivered in 24 patients, 15 patients received neo adjuvant chemotherapy, 7 patients had adjuvant chemotherapy and 2 patients received palliative chemotherapy. Intravenous paclitaxel 175 mg/m^2 plus carboplatin AUC-5 every 3 weekly. Survival curves were plotted for early stage (I/II) versus late stage (III/IV). Mean disease free survival in early stage 39.3 months (33.5-45.2 months) and late stage 12.9 months (7.7-18.2 months) (Figure 3). Mean overall survival in early stage 55.3 months (49.3-61.2 months) and late stage 21.1 months (15.5-26.8 months) (Figure 4). In survival curve significant difference noted between early and late stage of disease. Mean DFS of all stage 23.6 months (16.7-30.4 months) and median DFS of all stages 18 months, mean OS of all stage 35.4 months (27.1-43.7 months) and median OS of all stages 36 months.

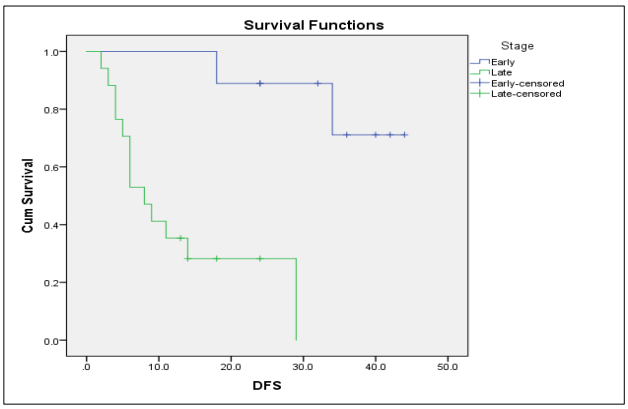

Figure 3: Disease free survival.

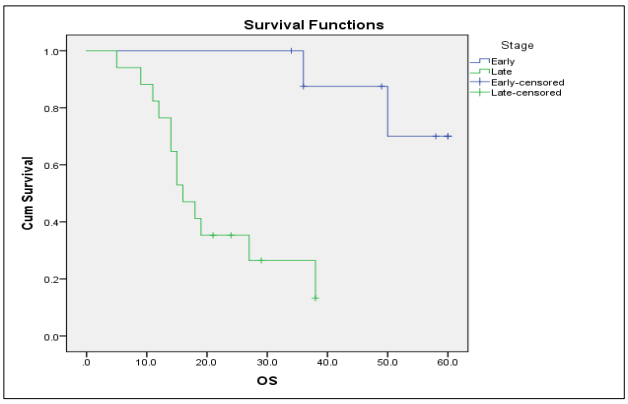

Figure 4: Overall survival.

DISCUSSION

Incidence of clear cell carcinoma varies from 5 to 25% based on geographic, race and ethnic factors. Asian population had highest incidence among all population.[1] ovarian clear cell carcinoma patients are younger and presents often at early stage compared with serous ovarian carcinoma subtype.[3,4] Median age at diagnosis 50.2 to 55.7 years, Presentation with pelvic masses usually upto 30 cm in size, mean size (13-15 cm), mostly unilateral tumours.[6] Histologically clear cytoplasm cells rich in glycogen. Microscopically classified as tubulo-cystic, papillary and solid.[2] Patients may also present with Para neoplastic and thromboembolic events. Many study had reported association between endometriosis and clear cell carcinoma ovary.[9] Molecular pathways and different alteration in clear cell carcinoma were mutations of AT–rich interaction domain 1A (ARID1A) 15-62% and phosphatidylinositol-4,5-bisphosphate 3-kinase (PIK3) catalytic subunit alpha (PIK3CA) 31.5-55%. Other alterations were histone deacetylase 6 and 7(HDAC 6 and 7), hepatocyte nuclear factor-1 beta (HNF-1b), MET overexpression or gene amplification 22-37%, mismatch repair gene dMMR 10-15%, AKT2 amplification (14%), germline BRCA 1 and 26%, KRAS mutation (5-10%), and PTEN 5-8%.[11,12]

Early stage (I and II) and late stage (III and IV). Patients with early stage had good prognosis, advanced disease had poor prognosis compared to those with serous high grade subtype.[14-16] The standard surgical treatment for early stage consists of bilateral salpingo-oophorectomy with total hysterectomy, peritoneal washings, peritoneal biopsies, infracolic omentectomy, bilateral pelvic and para–aortic lymphadenectomy.[17] European society of Medical oncology recommends adjuvant chemotherapy from stage IC2, it could be omitted with stage IA-IC1 who underwent comprehensive surgical staging.[18]

In advanced stage primary cytoreductive surgery followed by paclitaxel + carboplatin based chemotherapy is the standard approach, if resection of all macroscopic disease with major morbidity and mortality.[19] Neo adjuvant chemotherapy followed by interval debulking surgery is an alternative option, it should be reserved for patients who are at high risk for major postoperative complication and mortality due to elderly age, poor performance status, comorbids, fraility, malnutrition, disseminated disease less likely for optimal debulking.[20,21] Single-center Taiwan study reported lower survival rate compared with high-grade serous carcinoma in advanced stage (stage III 22.3% versus 47.3%, p=0.001, stage IV=0% versus 24.4%, p=0.001). Indian study Kaur et al analysed relapse pattern and survival analysis in Indian population.[22] First line platinum chemotherapy response is low (11-50%) compared with high-grade serous subtype (73-81%).[19] Although response rate is low, paclitaxel + carboplatin is standard of care for clear cell carcinoma. Bevacizumab can be considered in concurrent and maintenance setting. Novel agents like immune check point inhibitors,

PI3K/AKT/mTOR, multi-target tyrosine kinase inhibitors are currently evaluated in clinical trial in newly diagnosed, persistent or recurrent ovarian clear cell carcinoma.[23,24]

Limitations

One of the primary limitations of this study is the small sample size, which included only 26 patients diagnosed with clear cell carcinoma of the ovary. While this sample provides valuable insights, it may not fully capture the heterogeneity and range of clinical outcomes associated with this cancer subtype. A larger cohort would offer a more robust statistical power and enable more definitive conclusions. The retrospective design of this study presents inherent limitations, such as potential biases in data collection and the reliance on existing medical records. Retrospective studies often face challenges related to incomplete or inconsistent data, which can affect the accuracy and reliability of the findings. In this study, data were extracted from medical records that may not have uniformly recorded all relevant clinical details, leading to potential information gaps. Given these limitations, future research should focus on conducting prospective studies with larger, more diverse patient populations.

CONCLUSION

Clear cell carcinoma ovary relatively uncommon cancer. This study provides a comprehensive analysis of clear cell carcinoma of the ovary, focusing on patient demographics, clinical presentation, treatment modalities, and survival outcomes. The findings highlight the aggressive nature of this subtype and the critical importance of early detection and optimal surgical intervention. Patients diagnosed at an early stage demonstrated significantly better OS and PFS compared to those diagnosed at advanced stages. The study also underscores the challenge of chemo resistance in advanced-stage disease, emphasizing the need for innovative treatment strategies. Given the limitations of this study, including its small sample size and retrospective nature, there is a compelling need for future research to build on these findings. Prospective studies with larger and more diverse patient populations are essential to validate the results and provide more robust statistical power. Additionally, research should focus on exploring molecular and genetic markers that can predict treatment response and prognosis, facilitating the development of personalized medicine approaches. Clinical trials investigating novel therapeutic strategies, such as PARP inhibitors and immunotherapies, are crucial for improving outcomes in patients with chemo resistant clear cell carcinoma. Furthermore, studies addressing the quality of life and supportive care needs of patients are vital to ensure comprehensive and holistic care.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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