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Research Article,

Clear Cell Carcinoma Of The Ovary: An Experience From A Regional Cancer Centre In Odisha.

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Abstract

Background: Clear cell carcinoma of the ovary (CCCO) shows unique clinical features. There is a remarkable difference in incidence among different ethnic populations. The reasons for these differences in incidence around the world are not known.
Aim and objectives: To evaluate the clinical characteristics of patients with CCCO and to determine the impact of the stage of the disease and the extent of surgery on the prognosis of those patients.
Materials and methods: A retrospective analysis of the cases of clear cell carcinoma of the ovary that were operated in the regional cancer centre, Cuttack, from January 2009 to December 2018, was performed to evaluate the clinical characteristics and prognostic factors of the patients.
Results: During this study period, the incidence of CCCO was found to be 1.92%. The most common age group was 40–50 years (mean age of 44.7 years). The most common modes of presentation were abdominal distention and pain in the abdomen. Most of the cases in this study belonged to stage III C (65%), making it the most common stage in this group. 20% of the patients within the study group were nulliparous and 35% were menopausal in status.40% of the tumours were >15 cm in size. Almost 28% were lymph node positive. None in stage I had positive lymph nodes. All the cases in stage III were positive for lymph nodes. So, in stage III, 38.5% were positive for lymph nodes. 17/20 had some form of chemotherapy, of which 45% had NACT. Survival curves differ significantly between the early and advanced stages of the disease. A trend of survival benefit is seen with complete cytoreduction.
Conclusion: There is a need for data regarding the incidence and specific clinicopathologic behaviour of clear cell carcinoma of the ovary in the Indian population. This is an attempt to compile the data from a single tertiary institute in eastern India over the past 10 years. This is a rare tumour and the chances of missing data are well accepted. The survival advantage of early-stage-diagnosed patients over late-stage patients is tremendous and hard to ignore. Combining the fact that clear cell carcinomas are associated with precancerous lesions like atypical endometriosis and atypical adenofibroma, there may be scope for screening. The mutational changes leading to malignancy in these precancerous lesions also need to be refined. As stated, complete cytoreduction is the key to survival advantage and the need for referral to a centre with proper expertise for the same needs to be emphasized.

Keywords: Clear cell carcinoma of the ovary; endometriosis; gynecologic oncology; recurrence.

Introduction:

Clear cell carcinoma (CCC) was initially termed "mesonerhroma ovarii' in 1939.[1] Since 1973, it has been strictly defined by the World Health Organization as lesions characterised by clear cells growing in solid/tubular, or glandular

patterns as well as hobnail cells.[2] Since then, many studies have characterised the distinctive behaviour of these tumours as compared with other histological subtypes of ovarian neoplasms. CCCO shows rather unique clinical features. There is a remarkable difference in incidence among different ethnic populations. A recent report from the United States showed that incidence rates for CCCO were 4.8% in whites, 3.1% in blacks, and 11.1% in Asians. [3] Overall, it is noted that CCCO is quite rare in western countries but not so uncommon in Asia. The reasons for these differences in incidence around the world are not known.[4] In this study, we aimed to evaluate the clinical characteristics of patients with CCC of the ovary and to determine the impact of the stage of the disease and the extent of surgery on the prognosis of those patients.

Materials and methods:

This study was done to collect the clinical details of CCCO retrospectively from the hospital record section of AHRCC over a period of 10 years from 2009 to 2018. Tumours were diagnosed as CCC if typical clear or hobnail cells growing in a papillary, solid, or tubulocystic pattern appeared in > 90% of all pathological specimens. Clinical and pathological details were collected. Presenting signs and symptoms, reproductive history, type of surgery, and tumour stage were retrieved from the record. All patients were restaged using the FIGO 2014 staging system. The resected lymph node counts were not considered for the completion of the lymphadenectomy. The patients underwent neoadjuvant and adjuvant chemotherapy as per the institutional policies were included. A follow-up evaluation was done every 3 months for the first 2 years, every 6 months for the next 3 years, and annually thereafter. Survival data was last calculated in January 2019. The endpoints selected for analysis included disease free survival (DFS) and overall survival (OS). DFS was defined as the time from surgery to the date of progression or recurrence, death, or last follow-up. OS was defined as the time from surgery to the date of death or last follow-up. A survival analysis comparison between early and advanced stages of disease and between complete and incomplete cytoreduction was done. Statistical analysis: Analysis was performed using the GraphPad Prism program. The distributions of clinicopathologic events were evaluated. The univariate survival analysis was based on the Kaplan–Meier method. The survival curves were compared using the log-rank test. A P value of <0.05 was considered significant.

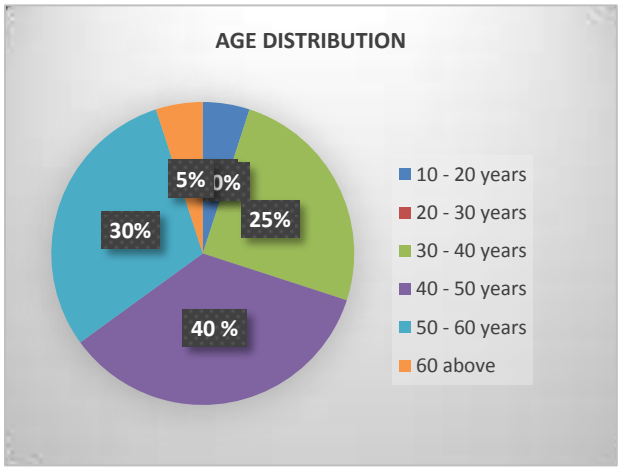

Figure 1 Age wise distribution of clear cell carcinoma cases.

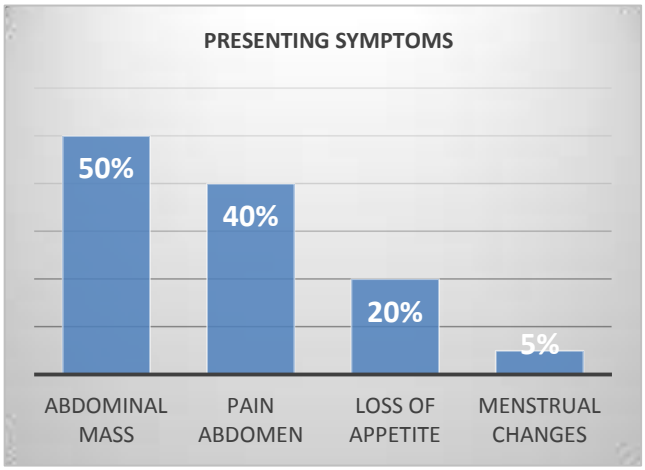

Figure 2 Presenting sign and symptoms.

Table 1 Clinicopathological characteristics of the clear cell carcinoma of ovary.

Clinicopathological characteristic	Numbers (%)
AGE	
10-20 years	1/20 (5%)

20-30 years	0/20 (0%)
30-40years	5/20 (25%)
40-50years	7/20 (35%)
50-60years	6/20 (30%)
60-70 years	1/20 (5%)
Presenting symptoms	
Abdominal distention/mass	10 /20 (50%)
Pain abdomen/bloating	8/20 (40%)
Loss of appetite	4 /20 (20%)
Menstrual changes	1 / 20 (5%)
Post menopausal	7 /20 (35%)
Primary amenorrhoea	1 /20 (5%)
Premenopausal	12/20 (60%)
Parity	
Nulliparous	4/20 (20%)
Multiparous	10/20 (50%)
Association with endometriosis	2/20 (10%)
Completion of cytoreduction	
CC 0	16 (80%)
CC 1	1 (5%)
CC 2	2 (10%)
Chemotherapy *	
Neoadjuvant chemotherapy	9/20 (45%)
Adjuvant chemotherapy	6/20 (30%)
CT only	1/20 (5%)

Results:

This study identified 20 cases of clear cell carcinoma of the ovary out of the 1040 cases of ovarian cancer, recorded over the study period from January 2009 to December 2018, in the Gynecological Oncology records of AHRCC, Cuttack. The incidence was calculated to be 1.92%.The most common age group among the cases identified was 40–50 years. The mean age was 44.7 years **[Figure 1] [Table 1].**

The most common modes of presentation were abdominal distention and pain in the abdomen. **[Figure 2]**. Most of the cases in this study belonged to stage III C (65%), making it the most common stage in this group. The rest belonged to stage I **[Figure 3] [Table 2].** Of the total cases, 20% of the patients within the study group were nulliparous and 35% were menopausal in status.

Ca 125 levels in the study group varied between 16 and 3455 IU/ml. The highest values were found in mixed serous and clear cell carcinomas. Value in stage 1 pure clear cell carcinoma was 54.5 IU/ml. The average value in stage 3 pure clear cell carcinoma was 198.4 IU/ml.

The tumours were mostly unilateral in origin. Regarding size, 40% of the tumours were ≥15 cm in size. **[Table 2]**

Table 2 Laterality and stage wise distributions.

Stage	Bilateral	Unilateral	Not defined	Total
I A	-	5	-	5
I C	-	2	-	2
III A	-	2	-	2
III C	6	2	3	11
Total(%)	6(30%)	11(55%)	3(15%)	20

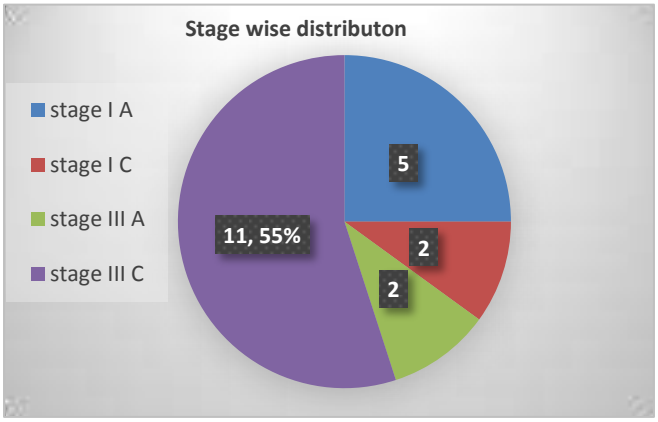

Figure 3 Pathological stage wise distribution.

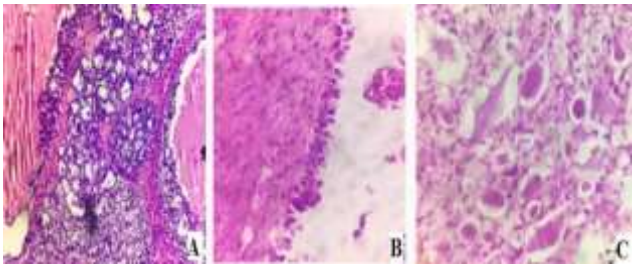

Figure 4 A : Scanner view showing typical tubulocystic arrangement of tumor cells.(10X,HE)
B: High power view showing nuclear hobnailing.(40X,HE).
C: High power view showing cells with clear cytoplasm and round nucleus. Good number of hyaline globules.(40X,HE)

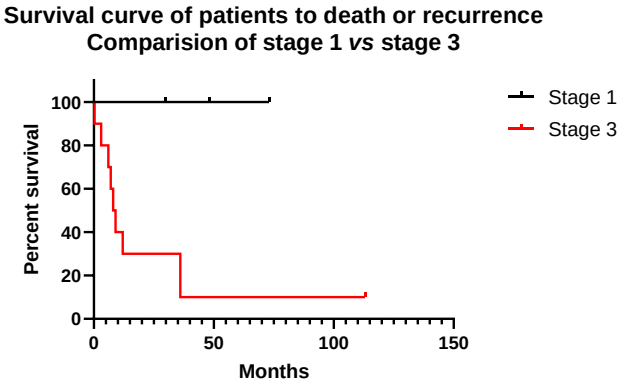

Figure 5 Comparison of Survival Curves

In total, 18 patients underwent complete surgical staging procedures, including hysterectomy, bilateral salpingoophorectomy, peritoneal washing, omentectomy, pelvic lymphadenectomy, and para-aortic lymphadenectomy. Nine were interval surgeries. One patient had failed primary and interval attempts at cytoreduction. The youngest member of the cohort had an attempt at fertility sparing and had a right salpingoophorectomy with right sided lymph node dissection and omentectomy (with a frozen section report as germ cell tumour). Apart from one surgery which was not completed, lymphadenectomy was omitted in one CC2 resection. All others had routine staging with an attempt at cytoreduction. **[Figure 4 A, B, and C]**

Of the 20, one patient had opened and closed during attempted primary as well as interval surgery due to dense adhesions. Our CC-0 resection rate was 80%. In the histopathological diagnosis, 18 of 20 were clear cell carcinomas of the ovary, and 2 cases were mixed clear cell with

serous. Histologically proven omental deposits were seen in 9 cases. None of the appendicectomy specimens showed evidence of disease. Out of the 18 cases where lymphadenectomy was done, 5 were positive. As a result, approximately 28% of those tested positive for lymph nodes.

Chemotherapy in some form was administered in 17 out of 20 cases. Neoadjuvant in 9, adjuvant in 6, and one patient had only chemotherapy as surgery was not possible. So, almost 45% had NACT. The regimens were as follows: intravenous paclitaxel 175 mg/m2 over 3 hours plus intravenous carboplatin area under the curve (AUC) 5 over 30 minutes on day 1; every 3 weeks for 3 to 8 cycles.

In two cases, there was a definite history of endometriosis. The 55-year-old, with primary amenorrhea, had non-canalization of the upper vagina and cervix with evidence of hematometra and bilateral hematosalpinges per op. She had a unilateral III C disease with CC-0 resection and was lost to follow-up after surgery. The 34-year-old had a history of surgery for endometriosis five years prior to presentation. She had a unilateral IA disease with CC-0 resection and was disease free for 4 years during the study period.

The youngest member of the cohort, a 15-year-old, underwent cytoreductive surgery for a unilateral disease and was post-operatively diagnosed with a high grade CCC with nodes positive for III A1 disease. She was given an attempt at fertility sparing and had a right salpingoophorectomy with right-sided lymph node dissection and omentectomy, as the frozen section reported a germ cell tumour. She defaulted after surgery, presented with extensive metastatic disease 7 months later, and died 9 months after diagnosis. She is the youngest reported case of CCC.

The survival curves of patients to death or recurrence were plotted, comparing stage I and stage III and also comparing complete versus incomplete cytoreduction surgery. Survival curves differed significantly between the early and advanced stages of the disease. Median survival for complete cytoreduction surgery was 12 months, whereas for incomplete cytoreduction, it was 8 months. A trend of survival benefit was seen with complete cytoreduction. **[Figure 5]**

Discussion:

There are significant geographic differences in the prevalence of CCC. According to studies in North America and Europe, the prevalence ranges from 1–12% [5,6,7,8], whereas in Japan, the prevalence ranges from 15–25%.[9,10,11] Data from the Japanese gynaecologic committee shows that the prevalence of CCC increased between 2002 and 2007 from 19% to 24.7% and it has been stabilised at 23% as per the latest reports. (10) CCC was diagnosed twice as frequently in Asian women in the United States (11.1% vs. 4.8% in whites).[12] The prevalence in our study population can only be stated in a prospective study. The incidence could be more, but never less than the calculated 1.92%. This could not be taken as representative of the incidence in the study population, as many of the early stage malignancies tend to be managed in the general gynecology department. In SEER data reported by Chan et al. (2008), women with clear cell histology were younger than patients with serous cancers (55 vs. 64 years; median age) [12]. Our cohort was younger, with 44.7 years as the mean age. The reason for the younger age of the cohort could be a sampling error. Considering that endometriosis leads to clear cell carcinomas, younger age is expected at presentation.

Ovarian CCC typically manifests as a pelvic mass.Recent reports involving large institutional cohorts compared low-stage to high-stage ovarian cancers (I/II vs. III/IV) and showed that 57–81% of CCC were diagnosed at stage I/II. [8,9] In a retrospective review done in Japan on more than 600 patients over 10 years, 49% of CCC were stage I compared to 17% of SC ,[9] and in SEER data, 56% of CCC were stage I compared to 19% for SC. [12] One of the reasons for the early detection was explained by the slow-growing tumour behaviour and the frequent presentation of the tumours as relatively large pelvic masses. The higher stage of presentation in the study cohort can be explained by the general trend towards late presentation, among the population the cohort is derived from. It is representative of the lack of awareness and also of the limited resources available to the population in question. Also, it could be that this study considered histological staging. Approximately 10% of clinical stage I/II tumours would be upstaged to stage III. [13]The majority of CCC tumours are unilateral, and the average size of a CCC is about 15 cm.In this cohort also, most were unilateral and 40% were of a size greater than or equal to 15 cm. An association between CCCO and endometriosis has been reported in many studies. Both atypical

endometriosis and atypical adenofibroma of the ovary have been considered precancerous lesions. [14, 15] The risk of CCCO was found to be significantly elevated in patients with endometrioma of the ovary as per Kobayashi et al. (relative risk = 12.4). [14] The risk increased significantly when the patients were diagnosed at an older age, especially over the age of 50, suggesting that the malignant change in endometriosis occurs near menopause. The K-ras mutation has been identified as one of the causes of endometriosis malignancy.[16] Additionally, PTEN mutations are also frequently observed (27.3%) in CCC, suggesting they are carcinogenesis-related genetic changes. [17] The most commonly associated mutations in endometriosis-associated ovarian cancers include a loss of heterozygosity in PTEN mutations (20%), beta-catenin gene mutations (16–54%), KRAS mutations (4–5%), microsatellite instability (13–50%), and ARID1A mutations (40–50%). [18, 19]

On the other hand, unlike HGSC, CCC is generally p53 wild type and has a lower frequency of BRCA 1 and BRCA 2 mutations. [13] In this series, the two cases identified as endometriosis leading to clear cell carcinoma had a long history of endometriosis. One with non-canalization of the outflow tract with primary amenorrhea presenting at 55 years, the other with surgery for endometriosis 5 years before presentation presenting at 34 years. In the Indian study by Kaur et al.,[20] 13.7% of women with ovarian clear cell carcinoma had endometriosis as confirmed by histopathological evaluation. We need a prospective study to correctly delineate the incidence of CCC with endometriosis and the behaviour of the tumour in the particular group. Lymph node positivity was seen among 28% of the patients who had lymphadenectomy done. It is suggested that it is important to evaluate the lymph node status through complete surgical staging procedures in CCC patients. A study of a large number of clear cell carcinomas revealed lymph node metastasis was documented in 3 out of 36 patients (9%) in pT1a tumours, 7.1% in pT1c tumours, 13% in pT2, and 58% in pT3 tumours, respectively. [13] The median duration of followup was 12 months (range, 3–113 months) in this study. Large institutional cohorts have shown the median survival time was 31.8 months in those with Stage I or II disease, 12.7 months in those with Stage III disease, and 17.8 months in those with Stage IV disease.[13] In this present study, all of the stage I who also had a complete cytoreduction survived till the end of the study. The median survival of the stage III patients was 8.5 months. Takano et al.[13] found that patients with no residual tumour had significantly better progression-free survival than those with a tumour less than 1 cm (P = 0.04) or greater than 1 cm (P 0.01). Tang et al.[21] identified FIGO stage and tumour resistance to chemotherapy as independent prognostic factors in OCCC. These features are well known predictors of survival in EOC. Surprisingly, neither optimal cytoreduction nor lymphadenectomy was established as an independent prognostic factor in their study. In this present study, the median survival for complete cytoreduction surgery was 12 months, and for incomplete cytoreduction surgery it was 8 months. We could say that the trend of survival benefit is seen with complete cytoreduction. The Indian studies on clear cell carcinoma of the ovary by Kaur et al. [20] and Ghosh et al. [22] have added light to this rare disease in the Indian population. This study hopes to add to the information to make an Indian data for clear cell carcinoma of the ovary.

Conclusion:

There is a need for data regarding the incidence and specific clinicopathologic behaviour of clear cell carcinoma of the ovary in the Indian population. This is an attempt to compile the data from a single tertiary institute in eastern India over the past 10 years. This is a rare tumour and the chances of missing data are well accepted. The survival advantage of early-stage-diagnosed patients over late-stage patients is tremendous and hard to ignore. Combining the fact that clear cell carcinomas are associated with precancerous lesions like atypical endometriosis and atypical adenofibroma, there may be scope for screening. The mutational changes leading to malignancy in these precancerous lesions also need to be refined. As stated, complete cytoreduction is the key to survival advantage and the need for referral to a centre with proper expertise for the same needs to be emphasized.

Conflict of interest:Nil

Funding source:nil

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