Section: Gynaecological Oncology

Original Research Article

SURVIVAL ANALYSIS AND RECURRENCE PATTERNS OF EPITHELIAL OVARIAN CARCINOMA –A TERTIARY CARE CENTRE AUDIT

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Abstract

Background: Carcinoma ovary is the 8 Th common cancer in females. Up to 70% of epithelial ovarian cancers present in advanced stages (3&4) and in spite of advances in treatments the 5 year survival is reported to be 30% only in advanced stages. They are treated by primary surgery or neo adjuvant chemo therapy followed by interval cytoreduction. This study analyses the overall and progression free survival of epithelial ovarian cancers treated in a regional cancer centre in south India. **Materials and Methods:** Patient characteristics, Ca 125 levels, surgical details, neo adjuvant treatment details recurrence of disease and survival status of epithelial ovarian cancers operated in our Institute during the period 2015-16 were collected retrospectively from medical records. Data analysis were done using SPSS software. Total of 169 cases of epithelial ovarian cancers treated during this period were included in the study. Median age of patients was 51.6years.124 (73.4%) of women presented in stage 3c and 21(12.4%) in stage 4.Only 14 .2% presented in early stages. 35 (20.7%) patients were treated by primary surgery followed by chemotherapy.134 (79.3%) were treated by neo adjuvant chemo therapy followed by interval cytoreduction. Complete cyto reduction was achieved in 77.9 % of cases. HPR showed high grade serous histology in 83.4% of cases. Median follow up period was 48 months. **Result:** Overall survival probability was 81.4% at 36 months. Progression free survival at 3 years was 52.3 %(S.E 3.9) and mean progression free survival was 23 months. Initial ca 125 value <100 had a significant survival advantage compared to values >100 (85.9% vs 42%) (P value < 0.001). Progression free survival was longer in patients who achieved complete cyto reduction compared to those who had a sub optimal cyto reduction only and this difference in survival manifested mainly after 12 months after initial treatment. (P value-0.083). **Conclusion:** 3-year PFS was52.3% and mean progression free survival is 23 months in our cohort. Patients who had complete cyto reduction at surgery had had a better PFS compared to those complete cyto reduction was not achieved. Overall and Progression free survival of patients treated in our centre is comparable to national and international data.

INTRODUCTION

Globally around 3.14 lakhs new cases of ovarian cancers are reported each year with around 2 lakhs deaths by ovarian cancer in 2020. India reported 45,701 new ovarian cancer cases in the year 2020 ranking it the 8 Th common cancer in female. It contributes to 3.5% of cancer burden in India.[1]

Ovarian cancers are classified broadly into 4 broad groups namely epithelial ovarian tumours, germ cell and sex chord stromal and miscellaneous tumours,[2] 90% of these are epithelial ovarian cancers. The epithelial ovarian cancers are sub grouped into high grade serous (70%), endometriod (10%), clear cell (10%), mucinous (3%)and Low grade serous(<5%) and Brenner tumours(1%).[3]

Even though much effort has been put into developing effective screening strategies to diagnose the disease at an early stage, none of them has been highly promising. Still now majority of epithelial ovarian cancers present in stage 3 or 4 and 5 year survival relative survival is 48.6 %.[4] Due to recent

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advances in aggressive surgical techniques and chemotherapy there is some improvements in overall survival rates in Ca ovary over the past 20 years.[5]
Our study aims to assess the overall survival and progression free survival of epithelial ovarian cancers treated in a tertiary cancer care hospital in South India.

MATERIALS AND METHODS

This is a retrospective analysis of recurrence patterns and survival characteristics of epithelial ovarian cancers treated at a tertiary care cancer centre in India. Study protocol approved by the institutional review board (IRB no-10/2019/12, XXX, YYY) and data was collected from the medical records. Telephonic interviews were done to patients without adequate follow up records. We studied the clinical data and survival patterns of 169 patients with epithelial ovarian cancers treated during the period of two years from 2015-2016.

At initial presentation all patients were evaluated by tumour marker (Ca 125) and Contrast Enhanced CT abdomen and pelvis. Patient underwent primary surgery or ICR after assessing operability after clinical and radiological assessment. Complete cytoreduction was defined as no visible macroscopic deposits left behind at the end of surgery.

Those cases unfit for primary surgery due to poor ECOG status or had advanced stage disease at presentation (3C and 4) were taken up for neo adjuvant chemo therapy followed by interval cytoreduction after confirming the diagnosis by ascitic fluid cytology/Trucut biopsy from the peritoneal deposit or ovarian mass. Neoadjuvant chemotherapy with carboplatin AUC 5-6 and Paclitaxel 175mg /m2 dose were given for 3 cycles. They were re assessed after 3 courses of chemotherapy with CECT and marker response and taken up for surgery if clinically and radiologically operable. After surgery they received 3 more courses of adjuvant chemotherapy. Those patients with partial response to chemo who couldn't be taken up after 3 cycles of chemotherapy were reassessed again after 6 cycles of chemo with repeat contrast enhanced CT scan and CA 125 and decided for surgery if clinically and radiologically feasible for complete resection.

After finishing first line treatment they were kept on 3 monthly follow up for first 2 years and 6 monthly thereafter with Ca 125 and clinical examination. Imaging with USS/CT was done as indicated by symptoms or marker rise. Second line treatment for recurrent disease was initiated in these patients when they were symptomatic.

Patient characteristics such as age, parity, initial Ca 125, operative and pathology details and follow up data were collected from medical records. Overall survival (O.S) was calculated from the date of registration of patient to date of death either due to disease or any other cause or till last visit in those who are alive. Progression free survival (PFS) was calculated from time of registration at the Institute to date of starting treatment for recurrence if any.

Statistical data was analysed using SPSS version 14. Analysis was performed using SPSS software. Categorical variables were expressed using frequency and percentage. Continuous variables were expressed as mean and standard deviation. Overall survival (OS) and progression free survival (PFS) were calculated and Kaplan-Meier (KM) curves were constructed for overall and progression free survival calculation. Univariate comparisons of survival were done using log-rank tests.

RESULTS

A total of 169 cases of epithelial ovarian cancers treated by surgery and chemotherapy during this period were included in the study. Median age of our patients was 51.6 years. Majority of patients presented with abdominal distension (69.2%) or pain abdomen (52.1%).85.4% of cases presented in stage 3C or stage 4. [Table 1]

35 (20.7%) patients were initially treated by primary surgery followed by chemotherapy. In those managed by primary surgery, 24 (14.2%) patients were of early stage disease and comprehensive surgical staging was done for them. 11(6.5%) cases were with advanced disease and primary debulking surgery was done for them.134 patients were treated by NACT followed by ICR. Of these, 102 (76%) patients were showing good response to chemo therapy with marker response and tumour regression and ICR was done after 3-4 cycles of chemotherapy. The rest 32 (24 %) were taken up after 6 cycles of chemo. When operability was doubtful, laparoscopic assessment with Modified Faggotti scoring was done in 7 cases prior to opening abdomen.[6]

Complete cyto reduction was achieved in 113 /145 patients who were in advance stages, with a complete cytoreduction rate of 77.9%. Pelvic and Para aortic node dissection as part of staging was done in 19 cases and 14 cases of nodal debulking as part of ICR. And nodal positivity rate was 4.7% cases in surgically staged cases and 16.6% in ICR setting. (Refer [Table 2] for variables in treatment and pathological characteristics of the cohort)

73.6 % of women were diagnosed with ca ovary in stage 3 and 12% in stage 4. Early stage (stage 1& 2) cases were only 14.4%. Follow up details were available for 97.6% patients for of 36 months. Median follow up 48 months.

Recurrence Patterns

Patients were followed-up with Ca 125 and clinical examination 3 monthly for first 2 years and 6 monthly for next 3 years. Imaging with Ultra sound or CT was done as indicated by clinical findings or symptoms. Total of 91 patients (53.8%) developed recurrence of disease on follow up. Second line chemo was initiated when the patient was symptomatic. Relapse occurred in less than 6 months in 4.1% of patients,

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another 13% developed recurrent disease in 6-12 months and 36 % developed recurrence after 12 months. 52.7% of recurrences were loco regional 20% were nodal, 21% liver and sub diaphragm, 3% extra abdominal and of this, one case presented with brain metastasis and treated by palliative RT to brain. Second line chemo was received by 92.1% of these patients who developed relapse. 92% of patients were partially or fully sensitive to platinum Most commonly used second line chemo was a combination of Gemcitabine and Carboplatin (39%), re challenge with Carboplatin and Paclitaxel in 15.9%, Liposomal Doxorubicin (13.4%) or a combination of liposomal Doxorubicin and Carboplatin in 9.8% patients. Mean time for the progression free survival 2 was 6.8 months (Range 0-24 months).

45 patients (50% of them) developed second recurrence and 5(11%) patients progressed and succumbed to disease. These 45 patients received 3 rd. line chemo. Most common regimen used was liposomal Doxorubicin in 14 patients (31%). Mean PFS after 3rd line chemo was 3.6 months (Range 0-14). Subsequent recurrences occurred in 16 patients (35%) and further palliative chemotherapy was offered to them.

97.6% patients had a follow up data for 3 years with median follow up period of 49 months. Of total 169 patients 62 deaths occurred at 3 to 5 years. And overall survival probability at 3 years is 81.4 % (S.E 3). [Figure 1A]. Survival rates for early (stage 1&2) and advanced stages were calculated separately and plotted using the Kaplan Meir curve .We could see that stage 1&2 (combined) had 3 year and 5 year overall survival probability of 100 and 90.4% respectively. 3 year Overall survival was 80.5% and 5 year O.S 53.4% in stage 3. The 3 and 5 year Overall survival was 66.7% (S.E 10.3) and 48.4% (S.E 12) in stage 4. (P value 0.011) [Figure 1B].

91 patients developed recurrence at 3 years and 78 were censored. Probability of progression free survival at 3 years was 52.3 % (S.E3.9) and 42.2 (S.E 4.2) at 5 years. [Figure 2A] Stage wise PFS analysis showed a 3 and 5 year progression free survival of 100% and 85.5% in stage 1 and 2 (combined),where as in stage 3 , 3 and 5 year PFS was 48.6% (S.E 4.5) and 39.2(S.E 4.8) respectively. In stage 4 the PFS was 23.8% (S.E 9.3) at 3 years and 15.9 (S.E 9.0) at 5 years. (P value 0.001) [Figure 2B].

Factors Affecting PFS

Comparing the probability of progression free survival according to age, those patients who were <50 years had a better 3 year progression free survival compared to those above 50 years (61.9% vs 45.1% SE 5.1) (P value 0.12). Pre-menopausal women with carcinoma ovary had 3 year progression free survival probability of 61.7% (S.E 5.9) where as in post-menopausal women, PFS probability was 46.2 % at 3 years. (S.E-5.1) (P value 0.16).

Progression free Survival probability at 3 years was 55.1% (SE 4.3) and 44.5% (S.E 4.7 %) at 5 years for patients who achieved complete cyto reduction at surgery compared to 40.6% (SE 8.7) and 32.1% (S.E 8.9) for those who achieved sub optimal cyto reduction only. (P value 0.083) [Figure 3].

Significant Correlation of initial ca 125 value with survival was found in our analysis. When initial CA125 value was <100, survival at 3 years was 89.4%, whereas for Ca 125 values between 100-500,500-1000 & >1000 survival rates were 47.4%, 52.4% and 41.3% respectively. (P value <0.001). [Figure 4].

Presenting symptoms by patients (table 1)

Symptom	frequency	Percentage
abdominal distention	117	69.2
abdominal pain	88	52.1
Loss of appetite	53	31.4
Abnormal uterine bleeding	7	4.1
diagnosed at infertility evaluation	4	2.4
Dyspnoea	13	7.7
post-menopausal bleeding	4	2.4
Stage at presentation		
1	19	11.2
2	5	3
3c	124	73.4
4	21	12.4
Total	169	100

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Variables in treatment and pathological characteristics of epithelial ovarian cancer(Table 2)		
Median age at diagnosis	51.6yrs	
Primary surgery	35	(20.7%)
NACT followed by ICR	134	(79.2%)
Pre chemo ca 125 (mean)	2275	
Range	6 -51242)	
No of cycles of NACT		
3-4 cycles	102	(76.7)
6 cycles	32	(23.3%)
Post chemo CA 125 (mean)	391	(range 2-27125)
Complete Cyto reduction	113 /145	(77.9%)
Sub optimal cytoreduction	32 /145	22.1%
Histopathology		
High grade serous	141	(83.4%)
Clear cell carcinoma	4	(2.4%)
Endometriod carcinoma	13	(7.8%)
Mucinous carcinoma	9	(5.3%)
Low grade serous	2	(1.1%)
Extent of procedure		

Procedure	Number	Percentage
Hysterectomy	163	96.4
BSO(Bilateral salpingo oophorectomy)	169	100
Omentectomy	169	100
Partial Peritonectomy	73	43.2
Liver surface deposits excision	4	2.4
Sub diaphragm deposits excision	7	4
Splenectomy	2	1.2
Anterior resection	5	3
Pelvic+Para aortic nodes dissection/debulking	33	19.5

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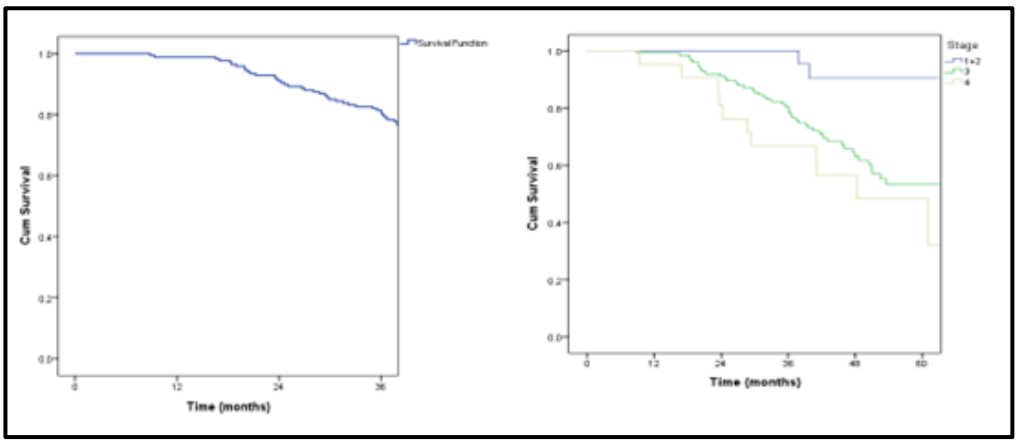

Figure 1: A-Kaplan Meir curve showing Overall survival, B-Kaplan Meir curve O.S Stage wise

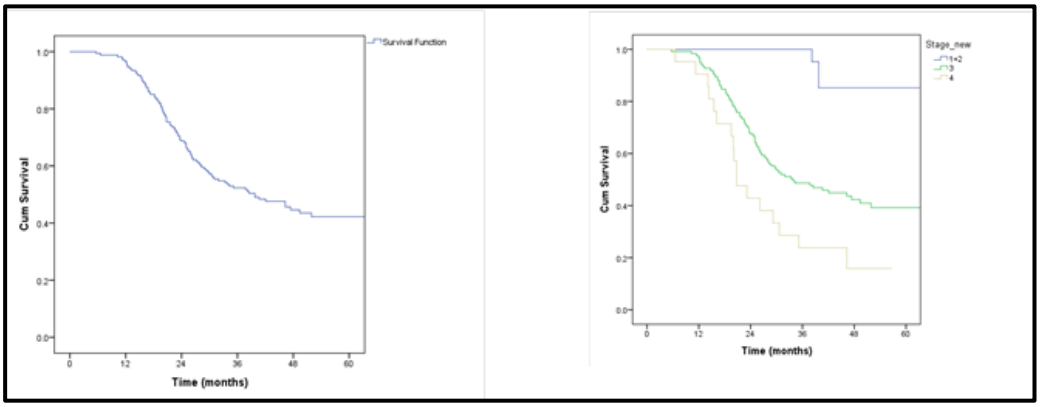

Figure 2: A-Kaplan meir curve showing PFS – Overall, B- PFS stage wise

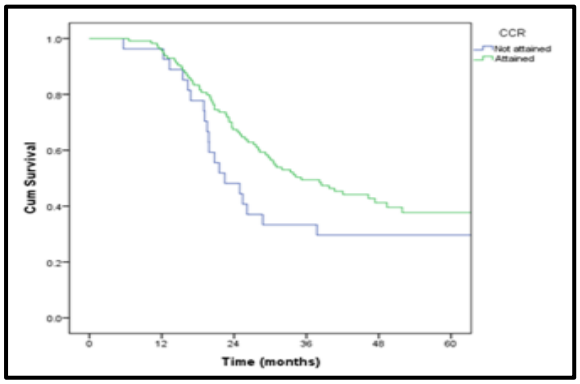

Figure 3: Relation between PFS and CCR

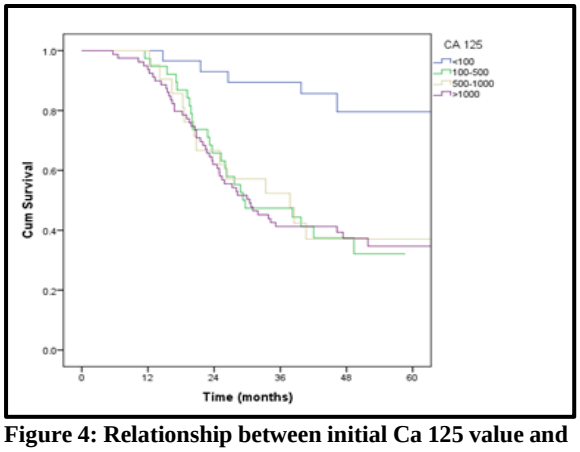

Figure 4: Relationship between initial Ca 125 value and overall survival

DISCUSSION

In our study group of patients, age group of the affected population was younger (median age 51.6years) compared to the average age for carcinoma ovary of 63 years as mentioned in western literature.[7] Various other Indian studies also show a similar age profile of our study population.[8,9] In a study from TATA Institute, the median age of their cohort was 52 years. In an analysis of changing trends in ca ovary N.S Murthy and S.Shalini showed that, the age specific incidence (ASIR) of carcinoma ovary increases after age of 35 and peaks between 55-64, as per data from different cancer registries across India.[10] The reasons for a younger age at presentation compared to western population might be further evaluated.

In our study 79.3 % patients presented in stage 3 c or stage 4 and treated initially by chemo therapy followed by ICR.20.7% patients were primarily surgically managed. 76% of patients treated by NACT –ICR showed good response to chemo and could be taken up for surgery after 3-4 cycles of chemotherapy. The complete cytoreduction rate was 77.9% in our study. Amita et al reports an optimal cytoreduction rate of 81.5% in their study.[11] Similar complete cyto reduction rates of 87.6% was reported by Viswanathan et all, in their data.[12]

Pelvic and para-aortic nodal dissection was done in 19.5% cases. Mean nodal count was 16 and nodal

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positivity in primary staging laparotomy was 4.7%. Nodal positivity rate in ICR setting was 16.6%. Our institute is following the policy of nodal debulking of enlarged nodes during ICR and not routine nodal dissection.[13] Study by M. Kleppe and T. Wang reports a nodal positivity rates in early ca ovary of 14.2% with 7.1% in para aortic region, 2.9% in pelvic region and 4.3% in both pelvic and para aortic region.[14] In our study, though the nodal count is considered adequate, nodal positivity was only 4.6% in staging procedures, and 16% in ICR in this study. Low number of primary cases might have affected the final nodal positivity rates here. Sites of relapse analysis showed that 20% of recurrences were nodal with para aortic nodes more commonly affected than pelvic nodes.

Relapse of disease occurred in 53.8% of patients during the follow up period of 60 months. 4.1% patients developed relapse in less than 6 months indicating a platinum resistant disease.13% patients were partially sensitive and 36% were having platinum sensitive disease. They received second line chemo as per institutional protocol. 39% patients received Carboplatin and Gemcitabine. Second most common regime used was Carboplatin and Paclitaxel in 15.9% and liposomal Doxorubicin in 13%.

Mean PFS 2 after second line chemo was 6.8 months.50% of these patients developed further relapse of disease and treated with further chemotherapy. Mean PFS 3 was 3.6 months in our study.

Overall survival analysis shows that in early stage disease the overall survival at 3 years and 5 years were 100% and 90.4% respectively. In stage 4, the O.S was 66.7% at 3 years and 48.4% at 5 years. The SEER data shows a 5 year Overall Survival rate of 92% in localised disease which is comparable to the present study.[7] In stage 3 the OS was 80.5% at 3 years and 53.4% at 5 years. The 5 year O.S in SEER data analysis shows a 30% O.S for distant disease and 47% when all stages are combined together.

The median progression free survival was 23 months in our study. Stage wise PFS analysis showed a 3 and 5 year progression free survival of 100% and 85.5% in stage 1 and 2 (combined). where as in stage 3,3 and 5 year PFS was 48.6%(S.E 4.5) and 39.2(S.E -4.8) respectively. In stage 4 the PFS was 23.8% (S.E 9.3) at 3 years and 15.9 (S.E 9.0) at 5 years. (P value 0.001). Amita et al reports a median PFS of 15.5 months in in advanced EOC from their data.[11] Vergote et al in their study of NACT versus Surgical debulking in advanced EOC reports a Median PFS of 12 months in their prospective analysis.[15]

Factors affecting PFS analysis showed a longer PFS for those less than 50 years compared to >50 years of age (61.9% vs 45.1%) and better PFS chance in pre-menopausal women compared to post-menopausal women (61.7% vs 46.2%). But this improved PFS was not statistically significant. Complete cytoreduction at surgery compared to suboptimal cytoreduction had a better PFS at 3 years (55.1% vs 44.5) (P value 0.083) and the difference in PFS manifested mainly after first 12 months after primary treatment. Initial Ca 125 levels less than 100 had a statistically significant relation with PFS at 3 years. (P value 0.001). Univariate analysis showed initial Ca 125 value less than 100 and post chemo fall of Ca 125 to normal levels had a statistically significant relation to progression free survival.

CONCLUSION

3 year PFS was52.3% and mean progression free survival is 23 months in our cohort. Patients who had complete cyto reduction at surgery had had a better PFS compared to those complete cyto reduction was not achieved. Overall and Progression free survival of patients treated in our centre is comparable to national and international data.

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