Section: Gynaecological Oncology

Original Research Article

# CLINICAL PROFILE AND SURVIVAL OUTCOME OF TYPE 1 AND TYPE 2 OVARIAN CANCERS-A COMPARATIVE STUDY IN A TERTIARY CANCER CARE HOSPITAL IN KERALA

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## Abstract

**Background:** Epithelial ovarian cancers consists of two major subtypes which differ in their histological patterns, mutations at molecular level, clinical behaviour, response to treatment. Type 1 Epithelial ovarian cancers consists of histological types of low grade serous carcinoma, Endometriod carcinoma and clear cell carcinoma behave less aggressively and present at earlier stages. Type 2 EOC which includes high grade serous EOC and undifferentiated tumours and carcino sarcomas. They behave in more aggressive ways clinically. **Materials and Methods:** Clinical presentations, treatments provided, follow up data for recurrence patterns and survival patterns of patients with these 2 types of epithelial ovarian carcinoma treated in a tertiary level cancer Institute in South India during the year 2016-2017 were collected retrospectively from medical records after approval from IRB. Survival analysis and log rank test were done and Kaplan Meier curves were plotted for analysis of overall and progression free survival for both types of EOC. **Result:** Overall survival and progression free survival was found to be much better in type 1 EOC. There was definite survival advantage in early stage type 1 EOC. In advanced stage this advantage was not seen and they also behaved aggressively in advanced stages. Similarly in type 2 EOC, though a small percentage of patients presented in early stages, survival was much better in early stages compared to advanced stage at presentation. **Conclusion:** Type 1 and 2 epithelial ovarian cancers have distinct clinical behaviour patterns, Type 1 tumours presenting early, less aggressive and have a better survival chance and they are relatively chemo resistant. Type 2 tumours are very aggressive, usually present late and more often require NACT followed by ICR due to their late presentations. They are more chemo sensitive but run an aggressive clinical course.

## INTRODUCTION

Incidence of ovarian cancer is around 3.14 lakhs cases globally in the year 2020 with around 2 lakh deaths.[1] Since majority of these tumours present at an advanced stage, mortality is high compare to other cancers in females like ca breast or endometrium.

Ovarian cancers can originate from the surface epithelium, germ cells, and sex chord –stromal cells or can be metastatic from other organs like colon, stomach or breast. Among all, EOC is the most common histological type amounting to 85 to 90 % of cases.[2] Epithelial ovarian cancers (EOC)consists of different histological types which differ widely in the clinical characteristics, stage at presentation, response to treatment, and survival probabilities. EOC are sub classified into histological types such as serous, Endometriod, mucinous, clear cell, Brenner tumours, epithelial stromal tumours like Carcinosarcomas and Adeno sarcomas.[3]

Recent research in the molecular genetic pathways have unravelled the mysteries in the pathogenesis of primary ovarian carcinoma and helped us to better understand the clinical behaviour and treatment plans. A dualist model for ovarian cancer was proposed by Dr Kurman highlighting the importance of new the molecular classification of carcinoma


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ovary into type 1& 2 and its integration into the current histologic classification.[4] This new model proposed division of type 1 tumours into 3 sub-groups namely 1) endometriosis related tumours that consists of Endometriod, clear cell and sero mucinous carcinomas. 2) Low grade serous carcinoma 3) Mucinous carcinomas and Malignant Brenner tumours.

Type 1 carcinomas usually present at an earlier stage as large unilateral cystic tumours. In this group all are considered low grade except clear cell carcinoma. They develop from benign precursor lesions on the surface of ovary which undergo malignant transformation later on. They usually present at an early stage and their prognosis is favourable when disease is confined to the ovaries, but few of them can present in advanced stages where the prognosis is poor.

Type 2 tumours mostly consists of high grade serous carcinomas, and Carcinosarcomas and undifferentiated tumours. They present in advanced stages in >75% of cases. They develop in the terminal end of fallopian tubes as serous tubal intra epithelial lesions (STIL) which progress on to STIC lesions and behave in aggressive manner with rapid spread into abdominal cavity presenting with massive extra ovarian disease on to omentum and upper abdomen even at presentation.[5] The volume of ovarian disease may be substantially low in type 2 tumours compared to type 1 but volume of extra ovarian disease much greater often with malignant ascites.

Molecular analytic studies using next generation sequencing techniques have shown that type 1 and 2 lesions harbour different kinds of distinct mutations which tell u that they are distinctly different lesions with different clinical behaviours. The main molecular genetic feature in type 2 tumours is the TP53 mutations and marked chromosomal instability in them. Whereas type 1 tumours harbour somatic mutations of PIK3CA (phosphatidyl inositol-4, 5 biphophate 3 kinase catalytic sub unit), PTEN (Phosphatase and Tensin homologue), Beta catenin1, K-RAS, B-RAF and ARID 1 A chromatin remodelling pathway mutation.[4]

In the present study we have examined the clinical profile and survival patterns of type 1 and 2 epithelial ovarian cancers and tried to compare the clinical outcomes and survival characteristics to one another.

## MATERIALS AND METHODS

This is a retrospective analysis of type 1 and 2 epithelial ovarian cancers operated at a tertiary cancer care hospital in Kerala from 2016 to 2017 for a period of two years. We studied type 1 and type 2 epithelial ovarian cancers treated during this period with primary surgery as well as Interval cytoreduction. All patients after initial clinical examination, were evaluated with Ca 125 and Contrast Enhanced CT abdomen and pelvis and assessed regarding operability, and decided regarding the line of management- primary surgery or interval cyto reduction. Those who were treated by primary surgery (staging laparotomy / primary cytoreductive surgery) received adjuvant by 6 cycles of paclitaxel and carboplatin as indicated.[6] Complete cytoreduction was defined as no visible macroscopic deposits left behind at the end of surgery. Patients with stage 3 c disease or poor ECOG status were initially treated with 3-4 cycles of neo-adjuvant chemo therapy and re-assessed for interval cyto reduction.

Histopathological confirmation by ascitic fluid cytology or guided biopsy from the omental deposits/ovarian mass was done prior to NACT. Neoadjuvant chemotherapy with carboplatin AUC 5-6 and Paclitaxel 175mg /M2 dose was given as first line treatment in them. Re assessment with Contrast enhanced CT and CA 125 levels done after 3 -4 courses of chemotherapy was done and decided for surgery if cases were operable as per review CT and if there was a fall in Ca 125. Rest of chemo completed after surgery to a total of 6 courses. Those patients who were not operable after 3-4 cycles of chemo were reassessed for surgery after 6 cycles of chemotherapy with repeat CT and CA 125 and taken up for ICR if radio logically feasible for complete resection. In doubtful cases laparoscopic evaluation was done to assess operability.[7,8]

After finishing first line of treatment, they were kept under 3 monthly follow up for first 2 years and 6 monthly thereafter. At follow up visits, they were questioned for any clinical symptoms, clinical examination performed and Ca 125 values were measured. Imaging was done when marker rise or when patient became symptomatic. Second line chemo therapy for recurrence was started when patients were symptomatic.

Patient's characteristics such as age, parity, initial Ca 125, details regarding type and extent of surgery (primary/ICR) and whether complete cytoreduction could be achieved or not was also noted. The pathology reports were reviewed and classified into two groups (type 1 and type 2). Endometriod carcinoma, mucinous, clear cell and low grade serous carcinoma were included in Type 1 epithelial ovarian cancers. High grade serous carcinoma, carcinosarcoma and undifferentiated tumours were classified into type 2 EOC.

Progression free survival (PFS) was calculated from time of registration at Institute to date of starting treatment for recurrence if any. Overall survival 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.

Statistical data was analysed using SPSS version 14. Categorical variables were described using mean and standard deviation. Overall survival and progression free survival curves were constructed using Kaplan –Meier method. Log rank test was used in univariate comparisons. P value <0.05 is said to be statistically significant.


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## RESULTS

Demographics and disease characteristics- comparison of type 1 and 2 cancers [Table 1].

**Table 1: ?.**

| | Type 1 (N- 28) | Type 2 (N – 141) |
|---|---|---|
| Age | | |
| < 50 Yrs. | 22 (78.6%) | 50 (35.5%) |
| > 50 Yrs. | 6 (21.4%) | 91 (64.5%) |
| Menopausal stats | | |
| Pre –Menopausal | 22 (78.6%) | 48 (34.3%) |
| Post-Menopausal | 6 (21.4%) | 92 (65.7%) |
| Presenting complaints | | |
| Abdominal distension | 16 (57.1%) | 101 (71.6 %) |
| Loss of appetite | 4 (14.3%) | 49 (34.3%) |
| Abdominal pain | 16 (57.1 %) | 72 (51.1%) |
| Abdominal uterine bleeding | 2 (7.1%) | 5 (3.5 %) |
| Infertility evaluation | 2 (7.1%) | 2 (1.4 %) |
| Post-menopausal bleeding | 1 (3.6 %) | 3 (2.1%) |
| Dyspnoea | 1 (3.6 %) | 12 (8.5%) |
| Stage at Presentation | | |
| Early(stage 1&2) | 16 (57.1%) | 8 (5.7%) |
| Late | 12 (42.9%) | 133 (94.3 %) |
| Initial Ca 125 levels | | |
| <100 U/ml | 15 (53.6%) | 15(10.6 %) |
| 100 – 1000 U | 7 (25%) | 53 (37.6 %) |
| >1000 U | 6 (21.4%) | 73(51.8%) |
| Post 3 cycles NACT Ca125 levels | | |
| <100 U | 4/7(57.1%) | 93(72.1%) |
| 100 – 1000 U | 3 (42.9 %) | 31(24.9 %) |
| >1000 U | 0 | 5 (3.9 %) |
| Complete Cytoreduction | | |
| Attained | 23(82 %) | 114 (80.9 %) |
| Not attained | 5 (17.9%) | 2 7(19.1%) |
| Surgery | | |
| Staging Laparotomy | 17 (60.7%) | 7(5%) |
| Primary cyto reduction | 4(14.3%) | 7(5 %) |
| Interval cyto reduction | 7 (25 %) | 127 (90.1%) |
| Histopathology | | |
| High grade serous Carcinoma | 141 (83.4%) | |
| Endometriod carcinoma | 13 (7.8%) | |
| Mucinous carcinoma | 9 (5.3 %) | |
| Clear cell carcinoma | 4 (2.4 %) | |
| Low grade serous carcinoma | 2 (1.1%) | |

**Table 2: Recurrence patterns**

| Time to recurrence | Type 1 EOC | Type 2 EOC |
|---|---|---|
| <6 months | - | 7 (4.9%) |
| 6-12 months | - | 22 (15.6%) |
| >12 months | 6 (21.4%) | 56(39.7%) |
| Total | 28 | 141 |

**Table 3: Sites of recurrence**

| Site of recurrence | Type 1 | Type 2 |
|---|---|---|
| Pelvis | 3(10.7%) | 25 (17.7%) |
| Peritoneum | 2 (7.1%) | 18 (12.8%) |
| Nodal | 1 (3.5%) | 19(13.4%) |
| Omentum | - | 6(4.1%) |
| Liver-sub capsular/parenchymal | - | 12 (8.5%) |
| Spleen | - | 2 (1.4%) |
| Extra abdominal | - | 2(1.4%) |
| Brain | - | 1(0.7%) |
| Total | 6/28 | 85/141 |

**Table 4: Second line chemo regimens used in type 1 versus type 2 EOC**

| Regimen | Type 1EOC | Type 2 EOC |
|---|---|---|
| Paclitaxel + Carboplatin | 3 | 11(13.75%) |
| Liposomal Doxorubicin +Carboplatin | - | 8 (10%) |
| Carboplatin +Gemcitabine | 1 | 43(53.75%) |
| Paclitaxel weekly | 1 | - |
| Etoposide oral | - | 3(3.75%) |


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| | | |
|---|---|---|
| Liposomal Doxorubicin | - | 11(13.75) |
| Carboplatin (single agent) | - | 3(3.75%) |
| Oxaliplatin +Capcitabine | 1 | - |
| Bevazisumab | - | 1(1.25%) |

Type 1 tumours presented at early stages (1 & 2) in 57.1% of patients where as in case of type 2 tumours. Only 5.7% presented in early stages. Majority of type 2 tumours presented in advanced stages (stage 3 -79.4 %, stage 4 -14.9%)

**Ca 125 levels at presentation.**

In 53.6% of type 1 tumours, Ca 125 levels were <100, only 21.4 % showed values >1000.

But in type 2 tumours, only 10.6% of patients had ca 125 <100, 24.1% with Ca 125 between 100- 500, 13.5% with 500-1000 and 51.8% presented with Ca 125 levels > 1000. 65% of patients with type 2 EOC had Ca125 values >500.

**Post chemo Ca 125 response**

Post chemo Ca 125 response is said to be a marker of chemo responsiveness of tumour. In majority of type 1 carcinoma primary surgical management was feasible and only 7/28 patients went for NACT and ICR After 3 cycles of NACT, values were <100 in 55.6% cases (4/7) This might be due to low chemo response of some type 1 tumours like clear cell and mucinous carcinoma. Where as in 72% of type 2 cases (N=93) Ca 125 values were <100 following 3-4 cycles of NACT. Post chemo ca 125 values remaining >1000 was seen in 5 patients (3.9%) of type 2 only. This is a predictable behaviour, as majority of type 2 EOC are aggressive tumours, respond to chemotherapy well initially, only to recur at a later date with more vigour.

**Complete cytoreduction**

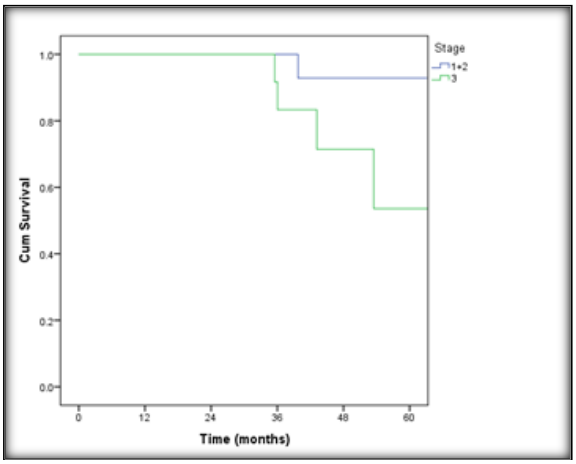
Complete cytoreduction was attained in 82.1% of type 1 and 80.9% of type 2 tumours. Probability of attaining complete cyto reduction was almost similar in two groups of our study. Here we should remember that 75% of type 1 tumours were treated by primary surgical line of management where as 90 % of type 2 EOC where managed by NACT followed by ICR.

**Type of surgery -comparison of type 1&2 tumours**

In type 1 tumours 75% cases were treated initially by primary surgery followed by chemotherapy. Whereas 90% of high grade tumours were treated by neo adjuvant chemo therapy followed by interval cyto reduction. This is due to the fact that type 1 tumours are less aggressive and presenting early at an operable stage where as majority of type 2 tumours are more aggressive and present at an advanced stage where an upfront surgery will not be feasible in most cases.

Among type 1 epithelial ovarian cancers we had 28 patients and 6(21.4%) patients developed recurrence on follow up, where as in type 2 cancers 85/141 (60.2%) developed recurrence of disease. IN type 1 EOC the proportion of patients developing recurrence was less and they recurred after 1 year in most cases .In type 2 tumours, recurrence occurred earlier.5% recurred in less than 6 months, and considered to be platinum resistant disease, an adverse prognostic factor in the survival of type 2 EOC. [Table 2]

**Overall survival of type 1 tumours according to stage of disease**




In type 1 tumours we had 16 cases in early stage (1&2) of which only 1 had recurrence of disease.3 year and 5 year survival probability was 100% and 92.9% (SE6.9) respectively. 12 patients presented in stage 3 of which 5 patients developed recurrence. No patients in our cohort presented in stage 4. In advances stages 3 & 5 year survival probability was 91.7 %( SE 8) and 53.6 %( SE18) respectively. Most recurrences occurred after 3 years.

**Overall survival of type 2 ovarian cancers**

In type 2 tumours we had only 8 /141(5.6%) patients in early stages and 1 patient developed recurrence on follow up. 112 (79.4%) patients presented in stage 3 and 44(31%) of them recurred after primary treatment and received second line chemotherapy with some succumbing to disease progression. In stage 3 disease, 3 year & 5 year Survival probability was 79.3 % (SE3.8) and 53.4 % (SE 5.4). In stage 4, 12/21(57.1%) developed recurrence on follow up. OS probability at 3 & 5 year was 66.7 % (S.E10.3) and 48.4 % (S.E12)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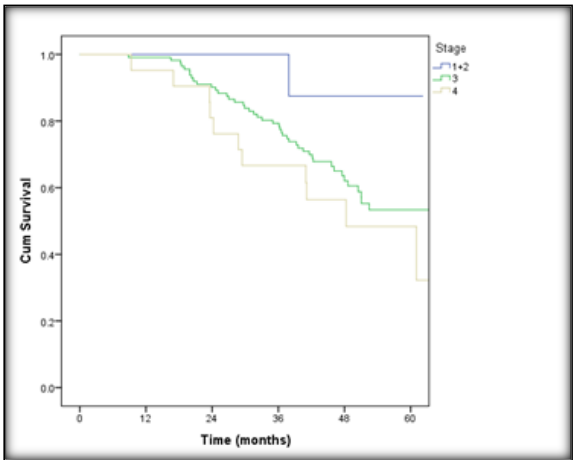
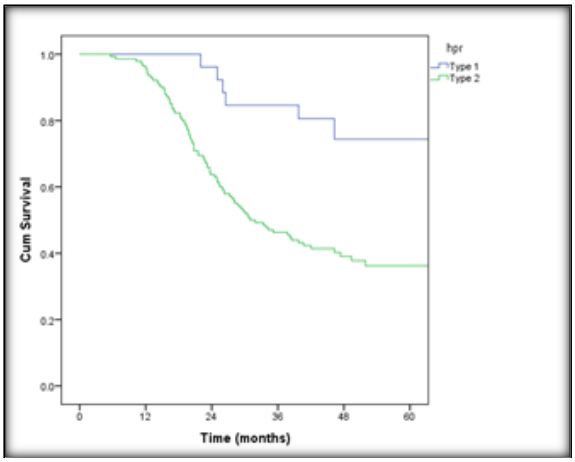


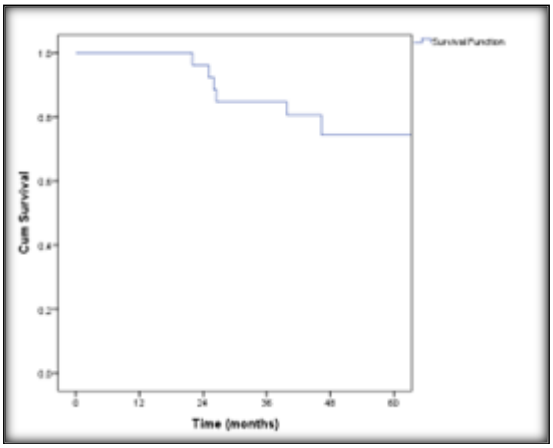

**Overall survival probability type 1 VS type 2 cancers**




Overall survival probability for type 1 ovarian cancers at 3 years is 84.6 % (SE7.1) and 5 year survival probability is 74.4%. (S.E9.3) In comparison type 2 cancers were more aggressive and their OS probability at 3 & 5 years is 46.3% (S.E 4.2) and 36.3% (S.E4.4). P value 0. 001.This is a significant observation showing the better O.S rates of type 1 in comparison to type 2 EOC.

**Progression frees survival type 1 ovarian cancers**

In type 1 cancers 6 patients developed recurrence on follow up and 3 year and 5 year PFS were 84.6% (S.E 7.1) and 74.4% (SE9.3) respectively.

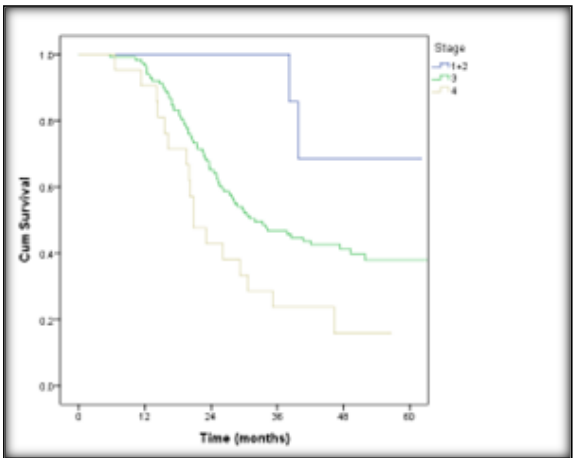



Type 2 ovarian carcinoma –Progression free Survival

In type 2 ovarian cancers 8 patients were there in early stage and 2 had developed recurrence. In advanced stage ( 3&4 ) there were 133/144 patients and 83 of them developed recurrence .

**PFS Type 2 –survival probability stage wise**

In early stage type 2 cancers the progression free survival at 3 and 5 years was 100% and 68.6% respectively. In stage III, 3 and 5 year progression free survival probability was 46.7% (S.E4.8) and37.9 %( SE 5).In stage IV, 3 year and 5 year progression free survival probability was 23.8 %( S.E9.3) and 15.9 %( S.E.9) respectively.




## DISCUSSION

Our institute is a high-volume centre in south India and caters to a population all over Kerala. Being a highly literate state majority of patients even from far off places were regular in follow up visits and were compliant to the instructions to them. So follow up data was available in great majority of patients. This analysis helped to audit our results of treatment outcomes and to compare our results with national and international data. This will also provide us the necessary in puts in patient counselling on what to expect with their treatment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outcome according to the different histological types.

Type 1 ovarian cancer patients presented at an earlier age compared to type 2 tumours. There was not much difference in the presenting symptoms among both groups. Proportion of patients with initial low levels of Ca 125 was seen in around 53% of our type1 ovarian EOC cohort where as in high grade serous cancers, only 10% had Ca 125 value below 100. Majority (90%) patients had values >100 to above 1000. 75% of type 1 cancers could be managed by initial surgery followed by adjuvant chemotherapy whereas only 10% cases of high-grade serous carcinoma could be taken up for primary surgery. Complete cytoreduction rates were almost similar around 80% in both the groups.

In early stages type 1 ovarian cancers are considered to be an indolent disease with good prognosis. But in advanced stages they also behave aggressively survival rates are low. E.Pawlik after analysing SEER data base had reported a 5 year survival of advanced type 1 EOC of 48 % only.(9).In our series of early stage type 1 EOC, 5 year survival was 93% and advanced type 1 EOC had a 5 year survival of 53.6% which is comparable to their data. During Neoadjuvant chemo therapy a poor chemo response may be manifested by type 1 EOC which might prompt the surgeon to think in line with the possibility of a type 1 EOC. Enomonto et all in their study has demonstrated that clear cell and mucinous carcinoma of ovary did not respond well to chemotherapy with carboplatin and paclitaxel. Response rate in advanced clear cell and mucinous carcinoma was 18% and 13% respectively only in their data.[10] 81% of serous and 89% of Endometriod carcinoma responded to chemotherapy in their series. Our data also had similar observations although the case numbers were low. Various other studies have also reported on the chemoresistane of clear cell carcinoma ovary.[11,12]

As an alternative, attempts to study the efficacy radiotherapy to clear cell carcinoma ovary are being tried, and suggests 20% improvement in a subset of stage 1 C and stage 2 cases of clear cell carcinoma.[13] Radiotherapy was used as a modality of treatment in 2 patients of our subset with clear cell carcinoma in recurrence with some benefit.

Further research with newer molecular targets is on in this area. PI3K, mTOR and AKT pathway alterations are found in molecular analysis of ovarian clear cell carcinoma.[14–16] Phosphorylated mTOR (a marker of activation) was expressed in 87% of specimens and report of Temsirolimus an MTOR inhibitor intravenously weekly treatment with 50% response was reported by Kikuchi et al in heavily treated recurrent clear cell carcinoma.[17] Such novel research targeted agents is underway and hopes to improve the survival outcome of type 1 EOC.

In type 2 EOC, only 5.7% presented in early stages (stage 1 & 2). 94.3% presented in advanced stages. If diagnosed in early stages, type 2 ovarian cancers are having a good 5 year survival outcome of around 76-92% as per SEER data.[18] Our data shows an overall 5 year survival of 85-92% and is in agreement. In advanced stages in spite of much efforts at newer innovations and drug trials, the improvement in mortality has not been very high. So we have a long way to go and future hopes should focus on research modalities to diagnose type 2 cancers in early stages so that we can bring up survival rates dramatically.

## CONCLUSION

Type 1 and 2 epithelial ovarian cancers have distinct clinical behaviour patterns, Type 1 tumours presenting early, less aggressive and have a better survival chance and they are relatively chemo resistant. Type 2 tumours are very aggressive, usually present late and more often require NACT followed by ICR due to their late presentations. They are more chemo sensitive but run an aggressive clinical course.

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